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(54) Title: GLYCOGEN SYNTHASE KINASE 3BETA INHIBITOR, COMPOSITION AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: Novel compounds having hydroxybenzoimidazole carboxylic amide are useful for inhibiting glycogen synthase kinase  $3\beta$  (GSK-3 $\beta$ ).



### GLYCOGEN SYNTHASE KINASE 3BETA INHIBITOR, COMPOSITION AND PROCESS FOR THE PREPARATION THEROF

#### Field of the Invention

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The present invention relates to a compound for inhibiting glycogen synthase kinase 3beta (GSK-3 $\beta$ ) activity, a pharmaceutical composition containing the compound as an active ingredient and a process for the preparation thereof.

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#### Background of the Invention

Glycogen synthase kinase 3 (GSK-3), the well-known target protein for the treatment of diabetes and dementia, is a serine/threonine protein kinase which inhibits the activity of glycogen synthase (GS) by way of phosphorylation.

In the fatty tissue of mice suffering from fatty diabetes, the GSK-3β activity has been observed to be 2 fold higher than that of a normal mouse (H. Eldar-Finkelman, *Diabetes*, 48:1662-1666 (1999)) and patients during the second type diabetes are characterized by a high expression level of GSK-3β than normal (S. E. Nikoulina et al., *Diabetes*, 49: 263-171 (2000)). Also, the GSK-3β activity in the brain of a dementia patient is high (Yamaguchi H. et al., *Acta. N europathol.*, 92: 232-241 (1996)), and transgenic mice programmed to express GSK-3β in the brain have abnormal neurons caused by hyperphosphorylating tau of the neurofibrillary tangle which plays an important role in the dementia attack (Lucas J. J. et al., *EMBO J.* 20: 27-39 (2001)).

GSK-3 $\beta$  is further related to bipolar disorder which can be treated by lithium and valproic acid, well-known GSK-3 $\beta$  inhibitors (Elahi S. et al., *J. Infect. Dis.* 176: 217-226 (1997)).

Thus, there has existed a need to develop an effective inhibitor of  $GSK-3\beta$  for treating or preventing  $GSK-\beta$ -dependent diseases.

The present inventors have endeavored to develop an effective inhibitor of  $GSK-3\beta$ ; and have unexpectedly found that a compound containing a hydroxybenzoimidazole carboxylic amide moiety can inhibit the activity of  $GSK-3\beta$ , and therefore, can be used for treating or preventing  $GSK-\beta$ -dependent diseases such as fatness, diabetes and dementia.

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#### **Summary of the Invention**

Accordingly, it is an object of the present invention to provide a GSK-3 $\beta$  inhibitor having high inhibitory activity against GSK-3 $\beta$ .

It is another object of the present invention to provide a process for preparing said inhibitor.

It is further object of the present invention to provide a pharmaceutical composition for inhibiting GSK-3 $\beta$ .

In accordance with one aspect of the present invention, there is provided a compound of formula (I), a pharmaceutically acceptable salt, hydrate, solvate or isomer thereof:

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$$(CH_2)_n$$
  $R^5$   $R^5$   $R^3$   $R^5$   $R^5$ 

wherein:

n is 0, 1, 2 or 3;

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen, hydroxy, halogen or morpholin-1-yl-ethylamino;

R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen;

linear or cyclic C1-C6 alkyl optionally having one or more substituents, the carbon of the alkyl being optionally replaced with nitrogen, sulfur or oxygen, wherein the substituent is: hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido; alkanesulfonyl; amido; an aromatic group optionally having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, alkylamino, carboxyl, amino, nitro, dioxoisoindole amido, sulfonylamino; an aromatic group having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido, the aromatic ring having nitrogen, sulfur or oxygen; or cyclic C<sub>3</sub>-C<sub>8</sub> alkyl optionally having one or more

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substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido;

an aromatic group optionally having one or more substituents, the aromatic ring having optional nitrogen, sulfur or oxygen, wherein the substituent is; hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido, alkanesulfonyl; amido; or linear or cyclic C1-C<sub>6</sub> alkyl optionally having one or more substituents, the alkyl having an optional nitrogen, sulfur or oxygen linkage and the substiuent of the alkyl being: hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido, alkanesulfonyl; amido; an aromatic group optionally having one or more substituents selected from the group consisting of hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; amido; dioxoisoindole; and a sulfonylamino having an aromatic group substituted with hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, sulfonylamido, alkanesulfonyl or amido; an aromatic group optionally having one or more substituents selected form the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, sulfonylamide, alkanesulfonyl and amido, the aromatic ring containing nitrogen, sulfur or oxygen; or a cyclic C3-C8 alkyl optionally having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido; or

form, together with the -N-(CH<sub>2</sub>)<sub>n</sub>- moiety to which they are attached, a nitrogen heterocycle optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, the heterocycle containing optional nitrogen or oxygen.

## **Detailed Description of the Invention**

Among the compounds of formula (I) of the present invention, the preferred are:

those wherein n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> have the same meaning as defined previously; R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen;

C<sub>1</sub>-C<sub>4</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, and an aromatic group, the aromatic group optionally having one or more substituents selected from the group consisting of OH, C<sub>1</sub>-C<sub>4</sub> alkyloxy, NH<sub>2</sub>, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino and dioxoisoindole; cyclic C<sub>3</sub>-

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C<sub>8</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>; C<sub>1</sub>-C<sub>4</sub> alkyl carrying a morpholine or oxopyrolidine group which is optionally substituted with OH, NH<sub>2</sub>, NO<sub>2</sub> or -O-; C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> aminoalkyl carrying a pyrrol, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, isoxazole, oxazole, isotiazole, tiazolidine, tiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, 1,2,5-thiodiazole, 1,2,3-thiodiazole, 1,3,4-oxadiazole, 1,3,4-thiodiazole, pyridine, pyrimidine or triazine group which is optionally having one or more substituents selected from the group consisting of Cl, OH, NH<sub>2</sub>, NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> and phenyl;

cyclic C<sub>3</sub>-C<sub>8</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>;

an aromatic group optionally having one or more substituents selected from the group consisting of OH; NH<sub>2</sub>; hydroxyalkyl; aminoalkyl; NO<sub>2</sub>; and a C<sub>1</sub>-C<sub>4</sub> alkyl group optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino, dioxoisoindole and thiophensulfonylamino; or

form, together with the -N- $(CH_2)_n$ - moiety to which they are attached, a nitrogen heterocycle optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>, the heterocycle containing 1 to 3 nitrogen, sulfur or oxygen atom.

In the present invention, the compounds of formula (I) as the below are most preferred:

25 those wherein n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> have the same meaning as defined previously; R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen;

C<sub>1</sub>-C<sub>4</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, morpholine, nitropyridineamino, pyridine, oxopyrolidin, imidazole optionally having a Cl, CH<sub>3</sub> or phenyl substituent; and phenyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, methoxy, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino and dioxoisoindole;

cyclic  $C_3$ - $C_8$  alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>;

phenyl optionally having one or more substituents selected from the group consisting of OH; NH<sub>2</sub>; NO<sub>2</sub>; and C<sub>1</sub>-C<sub>4</sub> alkyl optionally having a OH,

NH<sub>2</sub>, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino, dioxoisoindole or thiophensulfonylamino substituent; or

form, together with -N-(CH<sub>2</sub>)<sub>n</sub>- moiety to which they are attached, a piperidine ring optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>.

Important compounds of the present invention are listed in Table 1 below.

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Table 1

Com No.	n	$\mathbb{R}^1$	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
1	0	Н	Н	Н	Н	Н
2	0	Н	Н	Н	Н	Phenyl
3	0	H	Н	Н	Н	4-hydroxyphenyl
4	0	Н	Н	Н	Н	4-aminophenyl
5	0	H	H	Н	Н	4-hydroxycyclohexyl
6	0	Н	Н	Н	Н	4-(hydroxymethyl)phenyl
7	0	Н	Н	H	Н	4-(hydroxyethyl)phenyl
8	0	Н	Н	Н	Н	4-(aminoethyl)phenyl
9	0	Н	H	Н	Н	4-(p-toluenesulfonamidylethyl)phenyl
10	0	Н	H	Н	Н	4-(methanesulfonamidylethyl)phenyl
11	0	Н	Н	Н	Н	4-(phthalinidylethyl)phenyl
12	0	Н	Н	Н	Н	4-(2-thiophenylsulfonamidylethyl)phenyl
13	0	Н	Н	Н	Н	4-(ethansulfonamidylethyl)phenyl
14	0	Н	Н	CI	Н	phenyl
15	0	Н	Н	Cl	Н	4-hydroxycyclohexyl

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16	0	H	[ F	I C	Н	4-(p-toluenesulfonamidylethyl)phenyl
17	0	H	F	I CI	Н	
18	0	H	E	[ Cl	Н	4-(phthalinidylethyl)phenyl
19	0	H	F	[ Cl	Н	4-(2-thiophenylsulfonamidylethyl)pheny
20	0	Н	H	Cl	Н	4-(ethansulfonamidylethyl)phenyl
21	0	CI	H	Cl	Н	Н
22	0	Cl	H	Cl	Н	Phenyl
23	0	CI	H	CI	Н	4-hydroxycyclohexyl
24	0	Cl	H	Cl	Н	4-(aminoethyl)phenyl
25	0	Cl	H	Cl	Н	4-aminophenyl
26	0	Cl	H	Cl	Н	4-(hydroxymethyl)phenyl
27	0	Cl	H	Cl	Н	4-(hydroxyethyl)phenyl
28	0	Cl	H	Cl	Н	4-(p-toluenesulfonamidylethyl)phenyl
29	0	C1	H	Cl	Н	4-(methanesulfonamidylethyl)phenyl
30	0	C1	Н	C1	Н	4-(phthalinidylethyl)phenyl
31	0	C1	Н	Cl	Н	4-(2-thiophenylsulfonamidylethyl)phenyl
32	0	C1	Н	Cl	Н	4-(ethansulfonamidylethyl)phenyl
33	0	H	Н	F	Н	4-(methanesulfonamidylethyl)phenyl
34	0	Н	H	F	Н	4-(p-toluenesulfonamidylethyl)phenyl
35	0	Н	H	F	Н	4-(ethansulfonamidylethyl)phenyl
36	0	Н	H	F	Н	4-morpholinophenyl
37	0	F	H	F	Н	4-(methanesulfonamidylethyl)phenyl
38	0	F	Н	F	Н	4-(p-toluenesulfonamidylethyl)phenyl

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39	0	F	Н	F	H	4-(ethansulfonamidylethyl)phenyl
40	0	Cl	H	F	Н	4-(p-toluenesulfonamidylethyl)phenyl
41	0	Cl	H	F	H	4-(methanesulfonamidylethyl)phenyl
42	0	Cl	H	F	H	4-(ethansulfonamidylethyl)phenyl
43	0	H	Cl	F	H	4-(p-toluenesulfonamidylethyl)phenyl
44	0	H	Cl	F	H	4-(ethansulfonamidylethyl)phenyl
45	0	H	Cl	F	H	4-(methanesulfonamidylethyl)phenyl
46	0	H	Н	Н		$R^4$ , $R^5$ = piperidinyl
47	0	H	Н	Cl		$R^4$ , $R^5$ = piperidinyl
48	0	Cl	Н	C1		$R^4$ , $R^5$ = piperidinyl
49	1	H	Н	H	Н	4-nitrophenyl
50	1	H	Н	H	Н	4-aminophenyl
51	1	H	н	H	Н	phenyl
52	1	Н	н	Cl	н	phenyl
53	1	Н	н	Cl	Н	4-nitrophenyl
54	1	Н	Н	C1	Н	4-aminophenyl
55	1	Cl	Н	Cl	н	phenyl
56	1	Cl	Н	Cl	Н	4-nitrophenyl
57	2	Н	H	Н	Н	phenyl
58	2	Н	Н	Н	Н	4-hydroxyphenyl
59	2	Н	Н	Н	Н	4-nitrophenyl .
60	2	Н	Н	Н	Н	4-aminophenyl
61	2	Н	H	Н	Н	amino

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62	2	H	H	H	H	4-hydroxy-3-methoxyphenyl
63	2	H	Н	Н	Н	3-hydroxy-4-methoxyphenyl
64	2	H	Н	H	Н	4-(methanesulfonamidyl)phenyl
65	2	H	Н	H	Н	4-(p-toluenesulfonamidyl)phenyl
66	2	H	H	Н	Н	4-morpholinyl
67	2	H	H	Н	Н	4-phthlimidophenyl
68	2	H	H	H	Н	4-(ethanesulfonamidyl)phenyl
69	2	H	Н	H	Н	4-nitro-2-pyridinylamino
70	2	H	Н	Н	Н	2-pyridyl
71	2	H	Н	Cl	Н	phenyl
72	2	H	H	Cl	H	4-nitrophenyl
73	2	H	Н	Cl	Н	4-aminophenyl
74	2	H	Н	Cl	Н	4-hydroxyphenyl
75	2	H	Н	Cl	Н	4-(methanesulfonamidyl)phenyl
76	2	H	Н	C1	Н	4-(p-toluenesulfonamidyl)phenyl
77	2	Н	Н	Cl	Н	3-hydroxy-4-methoxyphenyl
78	2	Н	Н	Cl	Н	N-morpholinyl
79	2	Н	Н	C1	н	4-phthalimidophenyl
80	2	Н	Н	Cl	Н	4-(ethanesulfonamidyl)phenyl
81	2	Н	Н	Cl	Н	4-nitro-2-pyridinylamino
82	2	Н	Н	Cl	Н	2-pyridyl
83	2	Н	Н	Cl	Н	4-imidazolyl
84	2	Н	Н	Cl	Н	4-hydroxyphenyl

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85	5 2	2   1	F	Н	CI	H	4-acetylamino-2-pyridylamino
86	5 2	2 1	H	Н	Cl	H	4-(4-methylpiperazin-1-yl-acetylamino)phenyl
87	/ 2	2 I	I	Н	CI	H	
88	2	F	I	Н	Cl	Н	4-(dimethylaminoacetylamino)phenyl
89	2	F	I	H	C1	Н	4-(diethylaminoacetylamino)phenyl
90	2	I	I	Н	Cl	Н	4-aminophenyl
91	2	F	[	H	Cl	Н	4-amino-2-pyridylamino
92	2	H	[	H	Cl	Н	4-(morpholin-4-yl-acetylamino)phenyl
93	2	H		H	Cl	Н	4-(N,N-dimethylamino)phenyl
94	2	H		H	C1	Н	4-(morpholin-4-yl-ethoxy)phenyl
95	2	Н		Н	Cl	Н	4-(4-methylpiperazin-1-yl-ethoxy)phenyl
96	2	H		H	Cl	Н	2-hydroxyphenyl
97	2	H	<u> </u> :	H	Cl	Н	2-methoxyphenyl
98	2	H	]	H	C1	Н	3-bromophenyl
99	2	C1	1	H	Cl	Н	phenyl
100	2	Cl	I	H	Cl	Н	4-nitrophenyl
101	2	Cl	I	HI	Cl	н	4-hydroxy-3-methoxyphenyl
102	2	C1	F	H	Cl	Н	3-hydroxy-4-methoxyphenyl
103	2	C1	F	I	C1	Н	amino
104	2	Cl	F	I	Cl	Н	4-hydroxyphenyl
105	2	Cl	I.	I	Cl	Н	4-(p-toluenesulfonamidyl)phenyl
106	2	Cl	H	I	Cl	Н	4-(methanesulfonamidyl)phenyl

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107	2	CI	H	CI	Н	4-phthlimidophenyl
108	2	Cl	H	Cl	H	4-morpholinyl
109	2	Cl	H	Cl	Н	4-(ethanesulfonamidyl)phenyl
110	2	Cl	H	Cl	H	4-nitro-2-pyridinylamino
111	2	Cl	H	C1	H	2-pyridyl
112	2	Cl	H	Cl	Н	4-(acetylamino)phenyl
113	2	Cl	Н	Cl	Н	4-(pentanoylamino)phenyl
114	2	Н	H	F	Н	4-(methanesulfonamidyl)phenyl
115	2	H	Н	F	Н	4-(p-toluenesulfonamidyl)phenyl
116	2	Н	Н	F	Н	4-(ethanesulfonamidyl)phenyl
117	2	н	Н	F	Н	4-(acetylamino)phenyl
118	2	Н	Н	F	Н	4-methylpiperazin-1-yl
119	2	Н	н	F	Н	4-morpholin-1-yl
120	2	Н	н	F	Н	4-(pentanoylamino)phenyl
121	2	Н	н	F	H	4-hydroxyphenyl
122	2	Н	Н	F	Н	4-nitro-2-pyridinylamino
123	2	н	Н	F	Н	4-(methanesulfonylamino-2-pyridyl)amino
124	2	Н	н	F	Н	4-(p-toluenesulfonylamino-2-pyridyl)amino
125	2	н	н	F	Н	4-imidazolyl
126	2	н	н	F	Н	4-acetylamino-2-pyridylamino
127	2	Н	н	F	Н	4-(4-methylpiperazin-1-yl-
128	2	н	н	F	Н	acetylamino)phenyl 4-(4-ethylpiperazin-1-yl-acetylamino)phenyl

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129	2	H	Н	F	Н	4-(dimethylaminoacetylamino)phenyl
130	2	H	H	F	H	4-(diethylaminoacetylamino)phenyl
131	2	H	H	F	H	4-aminophenyl
132	2	Н	H	F	Н	4-morpholinophenyl
133	2	H	H	F	H	4-(3-dimethylaminopyrrolidin-1-yl)phenyl
134	2	H	Н	F	Н	4-(morpholin-4-yl-acetylamino)phenyl
135	2	H	Н	F	H	4-(N,N-dimethylamino)phenyl
136	2	H	H	F	H	4-(morpholin-4-yl-ethoxy)phenyl
137	2	H	H	F	H	2-hydroxyphenyl
138	2	H	Н	F	Н	2-methoxyphenyl
139	2	H	H	F	Н	3-bromophenyl
140	2	F	H	F	Н	4-(methanesulfonamidyl)phenyl
141	2	F	Н	F	Н	4-(p-toluenesulfonamidyl)phenyl
142	2	F	Н	F	н	4-(ethanesulfonamidyl)phenyl
143	2	Cl	Н	F	Н	4-(methanesulfonamidyl)phenyl
144	2	C1	Н	F	н	4-(p-toluenesulfonamidyl)phenyl
145	2	Cl	Н	F	Н	4-(ethanesulfonamidyl)phenyl
146	2	Cl	Н	F	н	4-(acetylamino)phenyl
147	2	Cl	Н	F	H	4-morpholin-1-yl
148	2	Cl	Н	F	Н	4-methylpiperazin-1-yl
149	2	Cl	Н	F	Н	4-(pentanoylamino)phenyl
150	2	Cl	Н	F	Н	4-hydroxyphenyl
151	2	Cl	Н	F	н	4-nitro-2-pyridinylamino
			_			

2 2	C	H	F	Н	4-(methanesulfonylamino-2-pyridyl)amino
3 2	C	H	F	Н	4-(p-toluenesulfonylamino-2-pyridyl)amino
2	Cl	H	F	Н	4-imidazolyl
2	CI	Н	F	Н	4-acetylamino-2-pyridylamino
2	Cl	H	F	Н	4-(4-methylpiperazin-1-yl- acetylamino)phenyl
2	Cl	Н	F	Н	4-(4-ethylpiperazin-1-yl-acetylamino)phenyl
2	Cl	H	F	Н	4-(dimethylaminoacetylamino)phenyl
2	Cl	Н	F	H	4-(diethylaminoacetylamino)phenyl
2	Н	Cl	F	Н	4-(p-toluenesulfonamidyl)phenyl
2	H	Cl	F	H	4-(methanesulfonamidyl)phenyl
3	Н	Н	Н	Н	methyl
3	H	Н	Н	Н	amino
3	H	Н	Н	Н	2-oxopyrrolidin-1-yl
3	Н	Н	H	Н	1-imidazolyl
3	Н	Н	H	H	4-N-morpholinyl
3	Н	Н	Н	Н	2-methylimidazol-1-yl
3	Н	Н	Cl	Н	methyl
3	Н	Н	Cl	н	2-oxopyrrolidin-1-yl
3	Н	Н	Cl	Н	1-imidazolyl
3	Н	Н	Cl	Н	4-morpholinyl
3	Н	Н	Cl	Н	2-phenylimidazol-1-yl
3	Н	Н	Cl	Н	4-methylimidazol-1-yl
	3 2 2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 3 3 3	2 C1 2 C1 2 C1 2 C1 2 C1 2 H 3 H 3 H 3 H 3 H 3 H 3 H 3 H 3 H 3 H 3	2 C1 H 2 H C1 2 H C1 3 H H 3 H H 3 H H 3 H H 3 H H 3 H H 3 H H 3 H H 3 H H 3 H H 3 H H 3 H H 3 H H	3         2         CI         H         F           4         2         CI         H         F           5         2         CI         H         F           6         2         CI         H         F           2         CI         H         F           2         CI         H         F           2         H         CI         F           2         H         CI         F           3         H         H         H           3         H         H         H           3         H         H         H           3         H         H         H           3         H         H         H           3         H         H         CI            3         H </td <td>3         2         Cl         H         F         H           4         2         Cl         H         F         H           5         2         Cl         H         F         H           6         2         Cl         H         F         H           2         H         Cl         F         H           3         H         H         H         H           3         H         H         H         H           3         H         H         H         H           3         H         H         H         H           3         H         H         H         H           3         H         H         H         H           3         H         H         Cl         H           3         H         H         Cl         H           3         H         H         Cl         H           <t< td=""></t<></td>	3         2         Cl         H         F         H           4         2         Cl         H         F         H           5         2         Cl         H         F         H           6         2         Cl         H         F         H           2         H         Cl         F         H           3         H         H         H         H           3         H         H         H         H           3         H         H         H         H           3         H         H         H         H           3         H         H         H         H           3         H         H         H         H           3         H         H         Cl         H           3         H         H         Cl         H           3         H         H         Cl         H <t< td=""></t<>

	_,					
174	3	Н	Н	Cl	Н	4,5-dichloroimidazol-1-yl
175	3	Н	H	Cl	Н	2-methylimidazol-1-yl
176	3	Cl	Н	Cl	Н	methyl
177	3	Cl	H	Cl	H	2-oxopyrrolidin-1-yl
178	3	Cl	H	C1	H	1-imidazolyl
179	3	Cl	H	Cl	H	4-morpholin-yl
180	3	Cl	H	Cl	Н	2-phenylimidazol-1-yl
181	3	Cl	H	Cl	Н	4-methylimidazol-1-yl
182	3	Cl	Н	Cl	H	4,5-dichloroimidazol-1-yl
183	3	Cl	Н	Cl	Н	2-methylimidazol-1-yl
184	3	C1	H	Cl	Н	2-isopropylimidazol-1-yl
185	3	H	Н	F	Н	1-imidazolyl
186	3	Н	Н	F	Н	2-isopropylimidazol-1-yl
187	3	Н	Н	F	Н	4-methylimidazol-1-yl
188	3	Н	Н	F	Н	2-methylimidazol-1-yl
189	3	Н	Н	F	Н	2-ethylimidazol-1-yl
190	3	Н	Н	F	Н	4,5-dichloroimidazol-1-yl
191	3	F	Н	F	Н	2-isopropylimidazol-1-yl
192	3	F	Н	F	Н	1-imidazolyl
193	3	F	Н	F	Н	4-methylimidazol-1-yl
194	3	F	Н	F	Н	4,5-dichloroimidazol-1-yl .
195	3	F	Н	F	Н	2-methylimidazol-1-yl
196	3	F	Н	F	Н	2-ethylimidazol-1-yl

	T	T-	$\overline{}$		Т	
197	3	F	H	F	H	4,5-dichloroimidazol-1-yl
198	3	C1	н	F	Н	1-imidazolyl
199	3	Cl	Н	F	Н	4-methylimidazol-1-yl
200	3	Cl	Н	F	Н	4,5-dichloroimidazol-1-yl
201	3	Cl	Н	F	Н	2-methylimidazol-1-yl
202	3	Н	Cl	F	Н	4-methylimidazol-1-yl
203	3	Н	Cl	F	Н	1-imidazolyl
204	3	$R^3 =$	mo	nd R <sup>4</sup> = rpholi /lamin	n-1-	4,5-dichloroimidazol-1-yl

The inventive compound (except for the compound wherein  $\mathbb{R}^3$  is morpholin-1-yl-ethylamino) of formula (Ia) may be prepared as in Scheme 1.

#### 5 Scheme I

wherein, p-TSA is p-toluenesulfonic acid, DMF is dimethylformamide, THF is tetrahydrofuran, TFA is trifluoroacetic acid, EDCI is ethyl-dimethylaminopropyl-carbodiimide hyrochloride, DMAP is 4-dimethylaminoprydine, HOBt is N-hydroxybezotriazole, n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the same meaning as defined previously.

As shown in Scheme I, the compound of formula (Ia) can be prepared by reacting 3-amino-4-methoxy benzoic acid (compound II) and an alcohol (e.g., methanol or ethanol) to obtain compound (III); adding anhydrous ptoluenesulfonic acid and benzonitrile to the compound (III) thus obtained, 10 refluxing the mixture at 80 to 200 °C, adding NaOCl thereto at room temperature and purifying by silica gel column chromatography to obtain compound (IV); dissolving the compound (IV) thus obtained in an alcohol (e.g., methanol or ethanol), adding an aqueous alkali solution (Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, K<sub>2</sub>CO<sub>2</sub> or KHCO<sub>3</sub> solution) thereto and refluxing the mixture to 15 obtain compound (V); dissolving the compound (V) thus obtained in an organic solvent, e.g., toluene, adding a Lewis acid (e.g., AlCl3 or BBr3) thereto and refluxing the mixture to obtain compound (VI); dissolving the compound (V) thus obtained in an alcohol, adding a strong acid, nitric acid or sulfuric acid, thereto at room temperature and refluxing the mixture to 20 obtain compound (VII); dissolving the compound (VII) thus obtained and (4bromomethylphenoxy)-methyl polystyrene Wang resin in an organic solvent, e.g., DMF, THF or chloroform, adding a base (CsCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub> or KHCO<sub>3</sub>) and KI thereto (1:3:3:3) and stirring the mixture at 50 to 60 °C for 1 to 24 hours to obtain compound (VIII); dissolving the 25 compound (VIII) thus obtained in an organic solvent, adding an alcohol solution of an alkali hydroxide (e.g., LiOH, NaOH or KOH) thereto and refluxing the mixture to obtain compound (IX); dissolving the compound (IX) thus obtained in an organic solvent, adding R<sup>4</sup>N(CH<sub>2</sub>)<sub>n</sub>R<sup>5</sup> and a coupling agent (e.g., EDCI/DMAP/HOBt, DCC or pyBop) thereto and stirring the 30 mixture at room temperature to obtain compound (X); and dissolving the compound (X) thus obtained in CH2Cl2, adding trifluoroacetic acid thereto and stirring the mixture at room temperature to obtain compound (Ia).

The inventive compound (wherein R<sup>3</sup> is morpholin-1-yl-ethylamino) represented to formula (Ib) may be prepared, as in Scheme II.

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#### Scheme II

As shown in Scheme II, the compound of formula (Ib) can be prepared by reacting 3-amino-4-methoxy benzoic acid (compound II) and an alcohol (e.g., methanol or ethanol) to obtain compound (III), adding ptoluenesulfonic acid, benzene and 4-nitrobezonitrile thereto, refluxing the mixture at 80 to 200 °C, adding NaOCl thereto at room temperature and purifying by silica gel column chromatography to obtain compound (XI); dissolving the compound (XI) thus obtained in an organic solvent, adding an aqueous alkali solution (e.g., Na<sub>2</sub>CO<sub>3</sub> solution) thereto, refluxing the mixture and purifying by silica gel column chromatography to obtain compound (XII); dissolving the compound (XII) thus obtained in an alcohol, adding Pd/C thereto and refluxing the mixture to obtain compound (XIII); dissolving the compound (XIII) thus obtained in an organic solvent, adding a base (e.g., CsCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub> or chloroethylmorphine and potassium iodide thereto and stirring the mixture at room temperature to obtain compound (XIV); dissolving the compound (XIV) obtained thus in an organic solvent, adding an alkali hydrate, stirring the mixture at room temperature to obtain compound (XV); dissolving the compound (XV) thus obtained in an organic solvent, adding 4,5-dichloro-1-(3-aminoprophyl)imidazole and a coupling agent (e.g., EDCI, DMAP or HOBt), stirring the mixture at room temperature and purifying by silica gel

column chromatography to obtain compound (XVI); and dissolving the compound (XVI) thus obtained in MC, adding a Lewis acid thereto, stirring the mixture, concentrating the resulting solution under a reduced pressure and purifying by silica gel column chromatography to obtain compound (Ib).

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A salt, hydrate, solvate and isomer of the inventive compound of formula (I) may be prepared by employing any of the known methods. The inventive compound of formula (I), a salt, hydrate, solvate or isomer thereof may used for the treatment of GSK-3 $\beta$ -dependent diseases including fatness, diabetes and dementia, by way of inhibiting GSK-3 $\beta$  activity, the inventive compound having an IC<sub>50</sub> value in the range of 1 to 10,000 nM.

Accordingly, the present invention includes a pharmaceutical composition which comprises a therapeutically effective amount of the compound of formula (I), a salt, hydrate, solvate or isomer thereof as an active ingredient and a pharmaceutically acceptable carrier; therefore, the pharmaceutical composition of the present invention exerts superior preventive and treating effects on GSK- $\beta$ -dependent diseases such as fatness, diabetes and dementia and the like.

A pharmaceutical formulation may be prepared in accordance with any of the conventional procedures. In preparing the formulation, the active ingredient is preferably admixed or diluted with a carrier, or enclosed within a carrier, sachet or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material acting as a vehicle, excipient or medium for the active ingredient. Thus, the formulations may be in the form of a tablet, pill, powder, sachet, elixir, suspension, emulsion, solution, syrup, aerosol, soft and hard gelatin capsule, sterile injectable solution, sterile packaged powder and the like.

Examples of suitable carriers, excipients, and diluents are lactose, dextrose, sucrose, sorbitol, mannitol, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, water, methylhydroxybenzoates, propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations may additionally include fillers, antiagglutinating agents, lubricating agents, wetting agents, flavoring agents, emulsifiers, preservatives and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after their administration to a mammal by employing any of the procedures well known in the art.

The pharmaceutical composition of the present invention can be administered via various routes including oral, transdermal, subcutaneous, intravenous and intramuscular introduction. In case of human, a typical daily dose of the compound of formula (I) may range from about 0.01 to 100 mg/kg body weight, preferably 0.1 to 50 mg/kg body weight, and can be administered in a single dose or in divided doses. However, it should be understood that the amount of the active ingredient actually administered ought to be determined in light of various relevant factors including the condition to be treated, the chosen route of administration, the age, sex and body weight of the individual patient, and the severity of the patient's symptom; and, therefore, the above dose should not be intended to limit the scope of the invention in any way.

The following examples are intended to further illustrate the present invention without limiting its scope.

<u>Preparation Example 1</u>: Preparation of Wang resin (p-benzyloxybenzyl alcohol resin)-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid ( $R^1 = H, R^2 = H$  and  $R^3 = H$ )

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(1) Preparation of 3-amino-4-methoxy benzoic acid methyl ester

3-amino-4-methoxy benzoic acid (40 g, 0.239 mol) was dissolved in methanol, H<sub>2</sub>SO<sub>4</sub> (38.14 ml, 0.717 mol) was added dropwise thereto and refluxed for 12 hours. The resulting mixture was cooled to room temperature and concentrated under a reduced pressure to remove methanol, neutralized with NaHCO<sub>3</sub>, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by recrystallization from ethyl acetate/hexane to obtain the title compound (39 g, 0.215 mol) in a yield of 90 %.

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<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.87-7.78 (2H, m), 7.22 (1H, d), 3.93 (3H, s), 3.82 (3H, s)

MW: 181

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(2) Preparation of 4-methoxy-3-[(N-chloro-benzimidoyl)-amino]-benzoic acid methyl ester

Anhydrous p-toluene sulfonic acid (41.99 g, 220.8 mmol) was 110.38 mmol) obtained in step 1 and benzonitrile (22.77 g, 220.8 mmol) were added thereto and stirred at 180 °C for 5 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The concentrate was dissolved in 50% methanol and 5% NaOCl (56 ml, 37.65 mmol) was added dropwise thereto. After 5 min, the resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chlomatography (eluent - MeOH/CDCl<sub>3</sub> = 5: 95, Merck, Silicagel 60) to obtain the title compound (31 g, 25.10 mmol) in a yield of 88%:

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.78 (1H, d), 7.48(1H, s), 7.37-7.24 (5H, m), 20 6.95 (1H, d), 3.78 (6H, s) MW: 318

(3) Preparation of 7-methoxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester

4-methoxy-3-[(N-chloro-benzimidoyl)-amino]-benzoic acid methyl ester (8 g, 25.10 mmol) obtained in step 1 was dissolved in 50 ml of 50% methanol and NaHCO<sub>3</sub> (5.32 g, 50.20 mmol) was added dropwise thereto at room temperature and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by recrystallization from ethyl acetate/hexane to obtain the title compound (6 g, 15.94 mmol) in a yield of 86 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.65 (1H, br), 8.23 (2H, d), 7.49 (3H, m), 6.75 (1H, d), 4.13 (3H, s), 3.99 (3H, s) MW : 282

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(4) Preparation of 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid

7-methoxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester (4.5 g, 15.94 mmol) obtained in step 3 was dissolved in 100 ml of toluene, aluminum chloride (9.56 g, 71.73 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (3.5 g, 13.77 mmol) in a yield of 86%.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.29 (2H, d), 7.68 (1H, d), 7.56-7.49 (3H, m), 6.67 (1H, d)
MW: 254

(5) Preparation of 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester

7-methoxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid (2.00 g, 7.46 mmol) obtained in step 4 was dissolved in 30 ml of methanol, H<sub>2</sub>SO<sub>4</sub> (2.00 ml, 37.28 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which purified by recrystallization from CHCl<sub>3</sub>/MeOH/hexane to obtain the title compound (1.7 g, 5.89 mmol) in a yield of 83 %.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 7.82 (1H, d), 7.42-7.25 (5H, m), 6.64 (1H, 30 d), 4.92 (3H, s)

MW: 268

(6) Preparation of Wang resin (p-benzyloxybenzyl alcohol resin)-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester

p-nitrophenyl carbonate Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 7-hydroxy-2-phenyl-1H-benzoimidazole-4-

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carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 5,  $Cs_2CO_3$  (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and  $CH_2Cl_2$  and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

(7) Preparation of Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester

Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 6 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O (2:1) was added thereto and refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

Preparation Example 2: Preparation of 2-(4-chloro-phenyl)-7-hydroxy-1Hbenzoimidazole-4-carboxylic acid ( $R^1 = H$ ,  $R^2 = H$  and  $R^3 = Cl$ )

- (1) Preparation of 3-[(4-chloro-N-chloro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester
- 25 Anhydrous p-toluene sulfonic acid (41.99 g, 220.76 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 of Preparation Example 1 and 4chlorobenzonitrile (22.78 g, 165.57 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding 1M NaHCO<sub>3</sub> thereto. 30 The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The concentrate was dissolved in 500 ml of 50% methanol and 5% NaOCl (197 ml, 132.46 mmol) was added dropwise thereto. After 5 min, the resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and 35 concentrated under a reduced pressure. The resulting residue was purified by silica gel column chlomatography (eluent - MeOH: CDCl<sub>3</sub> = 5:95,

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Merck, Silicagel 60) to obtain the title compound (19.43 g, 55.19 mmol) in a yield of 50%.

 $^{1}$ H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 7.62 (2H, m), 7.22-7.15 (4H, m), 6.59 (1H, s), 4.00-3.80 (6H, d) MW : 352

(2) Preparation of 2-(4-chloro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester

3-[(4-chloro-N-chloro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (5.5 g, 15.63 mmol) obtained in step 1 was dissolved in 40 ml of 50% methanol and Na<sub>2</sub>CO<sub>3</sub> (3.53 g, 33.26 mmol) was added dropwise thereto at room temperature and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (2.57 g, 8.13 mmol) in a yield of 52 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.15 (2H, d), 7.95 (1H, d), 7.51 (2H, m), 6.75 (1H, d), 4.06 (3H, s) MW: 316

- (3) Preparation of 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-25 carboxylic acid
- 2-(4-chloro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (1.0 g, 3.16 mmol) obtained in step 2 was dissolved in 10 ml of toluene, aluminum chloride (2.11 g, 15.8 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (745 mg, 2.59 mmol) in a yield of 82%.
- <sup>1</sup>H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 8.06 (3H, m), 7.50 (2H, m), 6.97 (1H, d) MW : 288

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- (4) Preparation of 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester
- 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (200 mg, 0.69 mmol) obtained in step 3 was dissolved in 5 ml of methanol, H<sub>2</sub>SO<sub>4</sub> (0.18 ml, 3.45 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with 1M NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel column chromatography (eluent MeOH / CDCl<sub>3</sub> = 5 / 95, Merck, Silicagel 60) to obtain the title compound (166 mg, 0.55 mmol) in a yield of 80 %.
- <sup>1</sup>H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 10.75 (1H, Br), 7.89 (3H, m), 7.46 (2H, d), 6.82 (1H, d), 3.39 (3H, s) MW : 302
- (5) Preparation of Wang resin-supported 2-(4-chloro-phenyl)-7-hydroxy-1H benzoimidazole-4-carboxylic acid methyl ester
- (4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in 5 ml of DMF, and 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.
  - (6) Preparation of Wang resin-supported 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid
- Wang resin-supported 2-(4-chloro-phenyl)-7-hydroxy-1H-35 benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O (1:1) was added thereto and the resulting mixture was refluxed

for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

- 5 <u>Preparation Example 3</u>: Preparation of 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = Cl$ ,  $R^2 = H$  and  $R^3 = Cl$ )
  - (1) Preparation of 3-[(2,4-dichloro-N-chloro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester

Anhydrous p-toluene sulfonic acid (20.99 g, 110.04 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (10 g, 55.20 mmol) obtained in step 1 of Preparation Example 1 and 2,4dichlorobenzonitrile (18.99 g, 110.04 mol) were added thereto and stirred at 180 °C for 6 hours. 15 The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO3 thereto. resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The concentrate was dissolved in 50% methanol and 5% NaOCl (30 ml, 20.64 mmol) was added dropwise thereto. After 5 min, the resulting mixture was extracted with 20 ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent - MeOH: CDCl<sub>3</sub> = 5:95, Merck, Silicagel 60) to obtain the title compound (18 g, 10.32 mmol) in a yield of 84%. 25

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.23 (1H, br), 7.75 (1H, d), 7.44 (1H, d), 7.36-7.26 (2H, m), 7.03 (1H, s), 6.88 (1H, d), 3.96 (3H, s), 3.76 (3H, s) MW: 318

- 30 (2) Preparation of 2-(2,4-dichloro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester
- 3-[(2,4-dichloro-N-chloro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (4 g, 10.32 mmol) obtained in step 1 was dissolved in 50 ml of 50% methanol and NaHCO<sub>3</sub> (2.19 g, 20.64 mmol) was added dropwise thereto at room temperature and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract

was concentrated under a reduced pressure. The resulting residue was purified by recrystallization from ethyl acetate/hexane to obtain the title compound (3.2 g, 5.47 mmol) in a yield of 88 %.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.54 (1H, d), 7.94 (1H, d), 7.48 (1H, s), 7.42 (1H, d), 6.76 (1H,d), 4.44 (3H, s), 3.99 (3H, s) MW: 351
- (3) Preparation of 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-10 carboxylic acid
  - 2-(2,4-dichloro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (1.9 g, 5.47 mmol) obtained in step 2 was dissolved in 100 ml of toluene, aluminum chloride (3.61 g, 27.05 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (1.63 g, 5.03 mmol) in a yield of 92%.
- <sup>1</sup>H NMR (DMSO- $d_6$ ): δ 8.19 (1H, d), 7.78 (1H, d), 7.62-7.55 (2H, m), 6.82 (1H, d) MW : 323
- (4) Preparation of 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4carboxylic acid methyl ester
- 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (1.63 g, 5.03 mmol) obtained in step 3 was dissolved in 30 ml of methanol, and H<sub>2</sub>SO<sub>4</sub> (1.08 ml, 20.12 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by recrystallization from ethyl acetate/hexane to obtain the title compound (1.5 g, 3.62 mmol) in a yield of 86 %.

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<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 11.42 (1H, br), 8.21 (1H, d), 7.89 (1H, d), 7.56 (1H, s), 7.38 (1H, d), 6.82 (1H, d), 3.99 (3H, s) MW: 337

5 (5) Preparation of Wang resin-supported 2-(2,4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

p-nitrophenyl carbonate Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol), obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

- (6) Preparation of Wang resin-supported 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid
- Wang resin-supported 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O (2:1) was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

<u>Preparation Example 4</u>: Preparation of Wang resin-supported 2-(4-fluorophenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = H, R^2 = H$  and  $R^3 = F$ )

- (1) Preparation of 3-[(4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester
- Anhydrous p-toluene sulfonic acid (41.99 g, 220.76 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 of Preparation Example 1 and 4-

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fluorobenzonitrile (20.00 g, 165.57 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent – MeOH: CDCl<sub>3</sub> = 5:95, Merck, Silicagel 60) to obtain the title compound (22.67 g, 75.06 mmol) in a yield of 68%.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.92-7.75 (4H, m), 7.15-7.02 (3H, m), 3.87-3.81 (6H, d) MW: 302
- (2) Preparation of 2-(4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-15 carboxylic acid methyl ester

3-[(4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (10 g, 34.48 mmol) obtained in step 1 was dissolved in 50% methanol and 5% NaOCl (61 ml, 41.38 mmol) was added dropwise thereto at room temperature. After 5 min, Na<sub>2</sub>CO<sub>3</sub> (7.31 g, 68.96 mmol) was added dropwise thereto and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (5.66 g, 19.65 mmol) in a yield of 57 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.18 (2H, t), 7.91 (1H, d), 7.30-7.25 (2H, t), 6.65 (1H, d), 6.85 (1H, d), 4.08 (3H, s), 3.98 (3H, s)
MW: 300

(3) Preparation of 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid

2-(4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (3 g, 10.00 mmol) obtained in step 2 was dissolved in toluene, aluminum chloride (6.67 g, 30.00 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (1.96 g, 7.20 mmol) in a yield of 72%.

<sup>5</sup> H NMR (MeOH-d<sub>4</sub>): δ 8.19-8.15 (2H, t), 8.06 (1H, d), 7.50-7.44 (2H, t), 7.00 (1H, d) MW: 272

(4) Preparation of 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-10 carboxylic acid methyl ester

2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (500 mg, 1.84 mmol) obtained in step 3 was dissolved in methanol, H<sub>2</sub>SO<sub>4</sub> (0.49 ml, 9.20 mmol) was added dropwise thereto and refluxed for 15 hours.

The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel chromatography to obtain the title compound (397 mg, 1.39 mmol) in a yield of 76 %.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 8.22-8.18 (2H, t), 7.80 (1H, d), 7.32-7.26 (2H, t), 6.70 (1H, d), 3.97 (3H, s) MW: 286

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(5) Preparation of Wang resin-supported 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

(4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

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(6) Preparation of Wang resin-supported 2-(4-fluoro-phenyl)-7-hydroxy-1Hbenzoimidazole-4-carboxylic acid

Wang resin-supported 2-(4-fluoro-phenyl)-7-hydroxy-1Hbenzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) 5 obtained in step 5 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O (2:1) was added thereto and the resulting mixture was refluxed The resulting solution was cooled to room temperature and for 5 hours. The filtrate was washed with MeOH and CH2Cl2, and dried to filtered. obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

Preparation Example 5: Preparation of Wang resin-supported 2-(2,4-difluorophenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = F, R^2 = H$ and  $R^3 = F$ )

(1) Preparation of 3-[(2,4-difluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester

Anhydrous p-toluene sulfonic acid (25.0 g, 137.43 mmol) was melted at 120  $\,^{\circ}$ C and 3-amino-4-methoxy benzoic acid methyl ester (10 g, 20 55.25 mmol) obtained in step 1 of Preparation Example 1 and 2,4difluorobenzonitrile (11.53 g, 82.87 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO3 thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over 25 MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (10.0 g, 31.22 mmol) in a yield of 57%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.31-8.22 (1H, m), 7.82-7.79 (1H, d), 7.65 30 (1H, s), 7.02-6.85 (3H, m), 3.88 (6H, s) MW: 320

(2) Preparation of 2-(2,4-difluoro-phenyl)-7-methoxy-1H-benzoimidazole-4carboxylic acid methyl ester 35

methyl ester (9.5 g, 29.66 mmol) obtained in step 1 was dissolved in 50% methanol and 5% NaOCl (53 ml, 35.71 mmol) was added dropwise thereto at room temperature. After 5 min, Na<sub>2</sub>CO<sub>3</sub> (6.29 g, 59.34 mmol) was added dropwise thereto and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (3.50 g, 11.0 mmol) in a yield of 37 %.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.99 (1H, bs). 8.65-8.57 (1H, m), .92 (1H, d), 7.10-6.97 (2H, m), 6.76 (1H, d), 4.13 (3H, s), 4.00 (3H, s) MW: 318
- (3) Preparation of 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid
- 2-(2,4-difluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (2.24 g, 7.04 mmol) obtained in step 2 was dissolved in toluene, aluminum chloride (3.75 g, 28.12 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (1.70 g, 5.86 mmol) in a yield of 83%.
- <sup>1</sup>H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 8.13-8.03 (2H, m), 7.47-7.33 (2H, m), 7.04 (1H, d) MW : 290
- (4) Preparation of 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-30 carboxylic acid methyl ester
- 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (1.70 mg, 5.86 mmol) obtained in step 3 was dissolved in methanol, SOCl<sub>2</sub> (8.2 ml, 112 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted

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with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel chromatography to obtain the title compound (1.50 mg, 1.64 mmol) in a yield of 84 %.

- <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.04 (1H, bs), .30-8.04 (1H, m), 7.73 (1H, d), 7.55-7.48 (1H, m), 7.33-7.27 (1H, m), 6.70 (1H, d), 4.01 (3H, s) MW : 304
- (5) Preparation of Wang resin-supported 2-(2,4-difluoro-phenyl)-7-hydroxy-10 1H-benzoimidazole-4-carboxylic acid methyl ester
  - (4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

(6) Preparation of Wang resin-supported 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid

Wang resin-supported 2-(2,4-difluoro-phenyl)-7-hydroxy-1H25 benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

<u>Preparation Example 6</u>: Preparation of Wang resin-supported 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = Cl$ ,  $R^2 = H$  and  $R^3 = F$ )

(1) Preparation of 3-[(2-chloro-4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester

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Anhydrous p-toluene sulfonic acid (41.99 g, 220.76 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 of Preparation Example 1 and 2-chloro-4-fluorobenzonitrile (25.76 g, 165.57 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (26.70 g, 79.47 mmol) in a yield of 72%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.92-7.75 (4H, m), 7.15-7.02 (3H, m), 3.87-3.81 (6H, d)

- 15 MW: 336
  - (2) Preparation of 2-(2-chloro-4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester
- 3-[(2-chloro-4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (10 g, 29.76 mmol) obtained in step 1 was dissolved in 50% methanol and 5% NaOCl (53 ml, 35.71 mmol) was added dropwise thereto at room temperature. After 5 min, Na<sub>2</sub>CO<sub>3</sub> (6.31 g, 59.52 mmol) was added dropwise thereto and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (5.17 g, 15.48 mmol) in a yield of 52 %.
- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.18 (2H, t), .91 (1H, d), 7.30-7.25 (2H, t), 6.65 (1H, d), 6.85 (1H, d), 4.08 (3H, s), 3.98 (3H, s) MW : 334
- (3) Preparation of 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-35 benzoimidazole-4-carboxylic acid
  - 2-(2-chloro-4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-

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carboxylic acid methyl ester (3 g, 8.98 mmol) obtained in step 2 was dissolved in toluene and aluminum chloride (5.99 g, 44.90 mmol) was added thereto, refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (1.87 g, 6.11 mmol) in a yield of 68%.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 8.19-8.15 (2H, t), 8.06 (1H, d), 7.50-7.44 (2H, t), 7.00 (1H, d) MW: 306

- (4) Preparation of 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester
- 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (500 mg, 1.63 mmol) obtained in step 3 was dissolved in methanol, H<sub>2</sub>SO<sub>4</sub> (0.43 ml, 8.15 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel chromatography to obtain the title compound (393 mg, 1.23 mmol) in a yield of 67 %.
- <sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 8.22-8.18 (2H, t), 7.80 (1H, d), 7.32-7.26 (2H, t), 6.70 (1H, d), 3.97 (3H, s) MW : 320
- (5) Preparation of Wang resin-supported 2-(2-chloro-4-fluoro-phenyl)-7-30 hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

(4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The

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filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

(6) Preparation of Wang resin-supported 2-(2-chloro-4-fluoro-phenyl)-7-5 hydroxy-1H-benzoimidazole-4-carboxylic acid

Wang resin-supported 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

- Preparation Example 7: Preparation of Wang resin-supported 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = H, R^2 = Cl$  and  $R^3 = F$ )
- (1) Preparation of 3-[(3-chloro-4-fluoro-benzimidoyl)-amino]-4-methoxy-20 benzoic acid methyl ester

Anhydrous p-toluene sulfonic acid (10 g, 52.57 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (3.88 g, 21.44 mmol) obtained in step 1 of Preparation Example 1 and 3-chloro-4-fluorobenzonitrile (5.0 g, 32.14 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (3.24 g, 9.62 mmol) in a yield of 45%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.96-7.95 (1H, m), 7.76-7.73 (2H, m), 7.60 (1H, bs), 7.17-7.11 (1H, m), 6.93(1H, d), 3.85(3H, s), 3.84 (3H, d)

35 MW: 336

- (2) Preparation of 2-(3-chloro-4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester
- 3-[(3-chloro-4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (3.24 g, 9.62 mmol) was dissolved in 50% methanol and 5% NaOCl (18 ml, 11.90 mmol) was added dropwise thereto at room temperature. After 5 min, Na<sub>2</sub>CO<sub>3</sub> (2.04 g, 19.25 mmol) was added dropwise thereto and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (0.95 g, 2.83 mmol) in a yield of 30 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.68 (1H, bs), 8.23-8.20 (1H, m), 7.96-7.91 (1H, m), 7.87 (1H, d), 7.27-7.20 (1H, m), 6.73 (1H, d), 4.10 (3H, s), 3.97 (3H, s)

MW: 334

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- (3) Preparation of 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-20 benzoimidazole-4-carboxylic acid
  - 2-(3-chloro-4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (0.95 g, 8.98 mmol) obtained in step 2 was dissolved in toluene, aluminum chloride (1.5 g, 11.25 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (0.81 g, 2.64 mmol) in a yield of 80%.
- <sup>1</sup>H NMR (MeOH-d<sub>4</sub>): δ 8.34 (1H, dd), 8.22-8.08 (2H, m), 7.62 (1H, t), 7.03 (1H, d)
  MW: 306
- (4) Preparation of 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-35 benzoimidazole-4-carboxylic acid methyl ester
  - 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-

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carboxylic acid (800 mg, 2.64 mmol) obtained in step 3 was dissolved in methanol, SOCl<sub>2</sub> (1.93 ml, 26.41 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel chromatography to obtain the title compound (690 mg, 2.15 mmol) in a yield of 81 %.

- <sup>1</sup>H NMR (DMSO- $d_6$ ): δ 12.39 (1H, bs), 8.56 (1H, d), 8.30 (1H, bs), 7.72 (1H, d), 7.59 (1H, t), 6.69 (1H, d), 3.90 (3H, s) MW : 320
- (5) Preparation of Wang resin-supported 2-(3-chloro-4-fluoro-phenyl)-7-15 hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester
  - (4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

(6) Preparation of Wang resin-supported 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid

Wang resin-supported 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-30 benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

Example 1: Preparation of 7-hydroxy-2-phenyl-1H-benzoimidazole-4-

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carboxylic acid amide  $(R^4R^5NH_2 = NH_4Cl)$ 

Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid (36 mg, 0.03 mmol) obtained in Preparation Example 1 was dissolved in 3 ml of DMF and aluminum chloride (5 mg, 0.09 mmol), EDCI (18 mg, 0.09 mmol), DMAP (11 mg, 0.09 mmol) and HOBt (12 mg, 0.09 mmol) were added thereto and the resulting mixture was stirred at room temperature. The resulting solution was filtered, the filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid amide.

Then, 30 mg of Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid amide was dissolved in 0.2 ml of CH<sub>2</sub>Cl<sub>2</sub>, 0.2 ml of trifluoroacetic acid was added thereto and stirred for 30 min. The resulting solution was filtered, the filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound in a yield of 90%.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 8.15 (2H, d), 7.84 (1H, d), 7.78-7.56 (3H, m), 6.83 (1H, m) MW: 253

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## Example 2 to 203

The same procedure as described in Example 1 was repeated using R<sup>4</sup>R<sup>5</sup>NH<sub>2</sub> listed in Table 2 to obtain the compounds 2 to 203, respectively.

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Com Pre Chemical cc No. No.  2 1 7-hydroxy-2-phe oimidazole-4-carl acid-phenylamide 3 1 7-hydroxy-2-phe benzoimidazole-4- 4 1 7-hydroxy-p	Chemical compound	R <sup>4</sup> N(CH <sub>2</sub> ) <sub>n</sub> R <sup>5</sup>	E	I NAME (I.S. 110, 110) WANTED	
νον ον					A CTAT
					1A <b>1</b> AA
	7-hydroxy-2-phenyl-1H-benz	aniline	0	8 8.10 (2H, d), 7.87 (1H, d) 7.85-7.60 (3H m)	320
П П	oimidazole-4-carboxylic				690
н н	nylamide			(F H1) 689 (m	
	7-hydroxy-2-phenyl-1H-	4-hydroxyanili	0	I, m), 7.98-7.82 (1H, d) 7.79-7.56	345
	benzoimidazole-4-carboxylic	ne			2
	acid(4-hydroxy-phenyl)-amide				
	7-hydroxy-2-phenyl-1H-	1,4-diaminoph	0	6 8.28-8.14 (2H, m), 8.03-7.91 (3H, m) 7.71-7.56 3	341
benzoimid	benzoimidazole-4-carboxylic	enylene		_	# 5
acid (4-an	acid (4-amino-phenyl)-amide		<del></del>		
5 1 7-hydroxy	7-hydroxy-2-phenyl-1H-	4-hydroxycycl	0	5 8.08 (2H, d), 7.82 (1H, d), 7.78–7 50 (3H m) 6 88 31	35.1
benzoimid	benzoimidazole-4-carboxylic	ohexylamine			100
acid(4-hyc	acid(4-hydroxy-cyclohexyl)-a			2.30–1.90 (4H, m). 1.85–1.20 (4H m)	
mide			<del></del>		
6 1 7-hydroxy	7-hydroxy-2-phenyl-1H-	4-(hydroxymet)	0	6 8.20 (2H, d), 7.92 (2H, d), 7.81-7.70 (1H m) 3F	350
benzoimida	benzoimidazole-4-carboxylic	hyl)aniline			 3
acid(4-hyd	acid(4-hydroxymethyl-phenyl)			(1H, m), 6.89 (1H, d). 4.65 (2H. s)	
-amide					

7-hy	7-hydroxy-2-phenyl-1H-	4-(hydroxyeth	0	6 8.14 (2H, d), 7.98 (1H, d). 7.78-7.60 (5H. m).	373
benzoim	benzoimidazole-4-carboxylic	yl)aniline			)
acid[4-	acid[4-(2-hydroxy-ethyl)-phe			(1H, t), 3.02 (1H, t), 2.81 (1H, t)	
nyl]-amide	ımide				
7-hy0	7-hydroxy-2-phenyl-1H-	4-(aminoethyl)	0	8 8.27-8.16 (2H, m), 7.95 (1H, d), 7.78 (2H, d),	372
penzo	benzoimidazole-4-carboxylic	aniline			
acid[	acid[4-(2-amino-ethyl)-pheny			(2H, t), 2.92 (2H, t)	
1]-amide	nide				
7-hy	7-hydroxy-2-phenyl-1H-	N-[2-(4-amin	0	6 8.20-8.02 (3H, m), 8.00 (2H, d), 7.70-7.68 (5H,	526
benz	benzoimidazole-4-carboxylic	o-phenyl)-eth			
acid	acid(4-[2-(toluene-4-sulfonyl	yl]-4-methylb		t), 2.73 (2H, t), 2.43 (3H, s)	-
amin	amino)-ethyl]-phenyl}-amide	enzenesulfona			
		mide			
					<del></del>
7-hy	7-hydroxy-2-phenyl-1H-	N-[2-(4-amin	0	6 8.13 (2H, d), 7.98 (1H, d), 7.75–7.53 (5H, m), 7.29	450
)ezo	bezoimidazole-4-carboxylic	o-phenyl)-eth	-		
ıcid	acid[4-(2-methanesulfonylami	yl]-4-methane			
10-e	no-ethyl)-phenyl]-amide	sulfonamide			

12	bezoimidazole-4-carboxylic acid {4-[2-(1,3-dioxo-1,3- dihydro-isoindole-2-yl)-ethyl]	honorall_other!	200 % 1117 00 T % 1100 00 0 ( 1117) k3 3 67 3	
12	acid {4-[2-(1,3-dioxo-1,3-dihydro-isoindole-2-yl)-ethyl]	pilensiz enisi	0./3-0.34 (4H, M), 0.30 (ZH, d), 5.89 (1H, d), 2.91	
12	dihydro-isoindole-2-yl)-ethyl]	-isoindole-1,3	(2H, t), 2.00 (2H, t)	
12		-dione		
12	-phenyl}-amide			
 	7-hydroxy-2-phenyl-1H-	thiophene-2- 0	8 8.15 (2H, d), 8.06 (1H, d), 7.80-7.55 (7H, m),	518
	benzoimidazole-4-carboxylic	sulfonic acid	7.23-7.10 (3H, m), 7.05 (1H, d), 3.16 (2H, t), 2.80	
	acid{4-[2-(thiophene-2-sulfon	[2-(4-amino-p	(2H, t)	
	ylamino)-ethyl]-phenyl}-amid	henyl)-ethyl]-		
	υ	amide		
13 1	7-hydroxy-2-phenyl-1H-	N-[2-(4-amin 0	8 8.17 (2H, d), 8.03 (1H, d), 7.77-7.68 (5H, m), 7.27	464
	benzoimidazole-4-carboxylic	o-phenyl)-eth	(2H, d), 7.01 (1H, d), 3.31 (2H, t), 2.99 (2H, q), 2.85	
	acid[4-(2-ethanesulfonylamino	yl]-ethanesulf	(2H, t), 1.23 (3H, t)	
	-ethyl)-phenyl]-amide	onamide		
14 2	2-(4-chloro-phenyl)-7-hydro	aniline 0	6 8.18 (2H, d), 8.11 (1H, d), 7.80 (2H, d), 7.67 (2H,	363
	xy-1H-benzoimidazole-4-carb		d), 7.40 (2H, t), 7.15 (1H, t), 6.89 (1H, d)	
	oxylic acid phenylamide			

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				T	<del></del>				<del></del>					 T				•-	
385				260					484					 536					
8 8.15 (2H, d), 7.84 (1H, d), 7.69 (2H, d), 6.90 (1H.	d), 3.95 (1H, m), 3.58 (1H, m), 2.28-1.95 (4H, m),	1.83-1.25 (4H, m)		5 8.18 (2H, d), 7.98 (1H, d), 7.80-7.60 (6H, m), 7.36	(2H, d), 7.16 (2H, d), 6.94 (1H, d), 3.09 (2H, t), 2.74	(2H, t), 2.41 (3H, s)			6 8.15 (1H, d), 7.94 (1H, d), 7.72 (2H, d), 7.62 (2H,	d), 7.28 (2H, d), 6.85 (1H, d), 3.32 (2H, t), 2.85	(3H,s), 2.84 (2H, t)			8 8.16 (2H, d), 8.02 (1H, d), 7.86-7.76 (4H, m),		(2H, t), 2.97 (2H, t)			
0	<del></del>			0					0					0					
4-hydroxycycl	ohexylamine	-		N-[2-(4-amin	o-phenyl)-eth	yl]-4-methyl-	benzensulfona	mide	N-[2-(4-amin	o-phenyl)-eth	acid yl]-methenesul	fonylamide		2-[2-(4-amino	-phenyl)-ethyl	]-isoindole-1,	3-dione		
2-(4-chloro-phenyl)-7-hydro	xy-1H-benzoimidazole-4-carb	oxylic acid (4-hydroy-	cyclohexyl)-amide	2-(4-chloro-phenyl)-7-hydro	xy-1H-benzoimidazole-4-carb	oxylic acid {4-[2-(toluene-4-	sulfonylamino)-ethyl]-phenyl}	-amide	2-(4-chloro-phenyl)-7-hydro	xy-1H-benzoimidazole-4-carb	oxylic acid	[4-(2-methanesulfonylamino-e	thyl)-phenyl]-amide	2-(4-chloro-phenyl)-7-hydro	xy-1H-benzoimidazole-4-carb	oxylic acid {4-[2-(1,3-dioxo	-1,3-dihydro-isoindole-2-yl)-	ethyl]-phenyl}-amide	
~			_	2					8					2		·			
15				16		-			17					18					

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xy-1H-benzoimidazole-4-carb sulfonic oxylic acid [2-(4-amin)] (4-[2-(thiophene-2-sulfonyla o-phenyl)-eth mino-ethyl)-phenyl]-amide yl]-amide xy-1H-benzoimidazole-4-carb o-phenyl)-eth oxylic [4-(2-ethanesulfonylamino-et onylamide hyl)-phenyl]-amide 3 2-(2,4-dichloro-phenyl)-7-hy ammonium 0 droxy-1H-benzoimidazole-4-c chloride arboxylic acid amide 3 2-(2,4-dichloro-phenyl)-7-hy amiline 0 droxy-1H-benzoimidazole-4-c chloride 3 2-(2,4-dichloro-phenyl)-7-hy aniline 0 droxy-1H-benzoimidazole-4-c arboxylic acid phenylamide 3 2-(2,4-dichloro-phenyl)-7-hy droxy-cyc 0 6 droxy-1H-benzoimidazole-4-c lohexylamine (1 arboxylic acid phenylamide arboxylic acid phenylamide acid phenylamide arboxylic acid phenylamide acid droxy-1H-benzoimidazole-4-c lohexylamine (1 arboxylic acid phenylamide acid (4-hydroxy-cyclohexyl)-amide	19	2	2-(4-chloro-phenyl)-7-hydro	thiophene-2-	0	6 8.15 (2H, d), 7.97 (2H, d), 7.75-7.57 (6H, m) 7 19	552
oxylic acid acid[2-(4-amin f4-[2-(thiophene-2-sulfonyla o-phenyl)-eth mino-ethyl)-phenyl]-amide yl]-amide yl]-amide xy-1H-benzoimidazole-4-carb o-phenyl)-eth oxylic acid amide hyl)-phenyl]-amide hyl)-phenyl]-amide hyl)-phenyl]-amide arboxylic acid amide arboxylic acid amide arboxylic acid amide arboxylic acid bhenylamide arboxylic acid phenylamide acid phenylamide acid arboxylic acid phenylamide acid acid phenylamide acid acid phenylamide acid acid acid acid acid acid acid acid			xy-1H-benzoimidazole-4-carb			(2H, d), 6.92 (1H, d), 3.17 (2H, t), 2.77 (2H, t)	
\frac{4-[2-(thiophene-2-sulfonyla o-phenyl)-eth mino-ethyl)-phenyl]-amide   yl]-amide   xy-[4-chloro-phenyl]-amide   xy-[4-chloro-phenyl]-7-hydro   \frac{7-(4-amin oxylic acid mide   hyl)-phenyl]-amide   hyl)-phenyl]-amide   hyl)-phenyl]-amide   arboxylic acid amide   arboxylic acid amide   \frac{2-(2,4-dichloro-phenyl)-7-hy ammonium odroxy-1H-benzoimidazole-4-c chloride   arboxylic acid phenylamide   \frac{2-(2,4-dichloro-phenyl)-7-hy aniline   0 droxy-1H-benzoimidazole-4-c chloride   \frac{2-(2,4-dichloro-phenyl)-7-hy aniline   0 droxy-1H-benzoimidazole-4-c chloride   \frac{4-hydroxy-cyc}{4-bydroxy-cyclohexyl)-amide   \frac{2-(2,4-dichloro-phenyl)-7-hy}{4-hydroxy-cyclohexyl)-amide   \frac{4-hydroxy-cyclohexyl)-amide   \frac{acid}{4-hydroxy-cyclohexyl)-amide   \frac{acid}{4-hydroxy-cyclohexyl)-acid   \frac{acid}{4-hydroxy-cyclohexyl)-acid   \frac{acid}{4-hydroxy-cyclohexyl)-acid   \frac{acid}{4-hydroxy-cyclohexyl)-acid   \frac{acid}{4-hydroxy-cyclohexyl)-acid   \frac{acid}{4-hydroxy-cyclohexyl)-acid   \frac{acid}{4-hydr				acid[2-(4-amin			
mino-ethyl)-phenyl]-amide yl]-amide  2			4-[2-(thiophene-2-sulfonyla	o-phenyl)-eth			
2 2-(4-chloro-phenyl)-7-hydro			mino-ethyl)-phenyl]-amide	yl]-amide			
xy-1H-benzoimidazole-4-carb o-phenyl)-eth oxylic [4-(2-ethanesulfonylamino-et   onylamide   hyl)-phenyl]-amide  3 2-(2,4-dichloro-phenyl)-7-hy   ammonium   o   droxy-1H-benzoimidazole-4-c   chloride   arboxylic acid amide   3 2-(2,4-dichloro-phenyl)-7-hy   aniline   o   o   droxy-1H-benzoimidazole-4-c   arboxylic acid phenylamide   3 2-(2,4-dichloro-phenyl)-7-hy   4-hydroxy-cyc   o   o   droxy-1H-benzoimidazole-4-c   lohexylamine   o   droxy-1H-benzoimidazole-4-c   lohexylamine   o   o   droxy-1H-benzoimidazole-4-c   ohexylamine   o   o   droxy-1H-benzoimidazole-4-c   ohexylamine   o   o   o   droxy-1H-benzoimidazole-4-c   ohexylamine   o   o   o   o   o   o   o   o   o	20	2	2-(4-chloro-phenyl)-7-hydro		_	6 8.17 (2H, d), 8.09 (2H, d), 7.73 (2H, d), 7.63 (2H.	498
oxylic  [4-(2-ethanesulfonylamino-et   y1]-ethanasulf  [4-(2-ethanesulfonylamino-et   onylamide   hyl)-phenyl]-amide  3			xy-1H-benzoimidazole-4-carb	o-phenyl)-eth	70		
[4-(2-ethanesulfonylamino-et hyl)-phenyl]-amide  2-(2,4-dichloro-phenyl)-7-hy ammonium 0 droxy-1H-benzoimidazole-4-c chloride arboxylic acid amide  2-(2,4-dichloro-phenyl)-7-hy aniline 0 droxy-1H-benzoimidazole-4-c arboxylic acid phenylamide  2-(2,4-dichloro-phenyl)-7-hy 4-hydroxy-cyc 0 droxy-1H-benzoimidazole-4-c lohexylamine arboxylic acid phenylamide  (4-hydroxy-cyclohexyl)-amide				yl]-ethanasulf		), 1.24 (3H, t)	
hyl)-phenyl]-amide  2-(2,4-dichloro-phenyl)-7-hy ammonium 0 droxy-1H-benzoimidazole-4-c chloride arboxylic acid amide  3 2-(2,4-dichloro-phenyl)-7-hy aniline 0 droxy-1H-benzoimidazole-4-c arboxylic acid phenylamide  3 2-(2,4-dichloro-phenyl)-7-hy 4-hydroxy-cyc 0 droxy-1H-benzoimidazole-4-c lohexylamine arboxylic acid phenylamide  4-hydroxy-cyclohexyl)-amide			[4-(2-ethanesulfonylamino-et	onylamide			
3 2-(2,4-dichloro-phenyl)-7-hy ammonium 0 droxy-1H-benzoimidazole-4-c chloride arboxylic acid amide 3 2-(2,4-dichloro-phenyl)-7-hy aniline 0 droxy-1H-benzoimidazole-4-c arboxylic acid phenylamide 3 2-(2,4-dichloro-phenyl)-7-hy 4-hydroxy-cyc 0 droxy-1H-benzoimidazole-4-c lohexylamine arboxylic acid phenylamide (4-hydroxy-cyclohexyl)-amide			hyl)-phenyl]-amide				
droxy-1H-benzoimidazole-4-c chloride  arboxylic acid amide  3 2-(2,4-dichloro-phenyl)-7-hy aniline 0  droxy-1H-benzoimidazole-4-c arboxylic acid phenylamide  3 2-(2,4-dichloro-phenyl)-7-hy 4-hydroxy-cyc 0 droxy-1H-benzoimidazole-4-c lohexylamine arboxylic acid arboxylic acid acid acid acid arboxylic acid	н	က	2-(2,4-dichloro-phenyl)-7-hy		<del> </del>	6 7.98-7.70 (2H, m), 7.69-7.52 (1H, m), 7.28-7.00	321
arboxylic acid amide  3			droxy-1H-benzoimidazole-4-c	chloride	<u>ن</u> —		
3 2-(2,4-dichloro-phenyl)-7-hy aniline 0 droxy-1H-benzoimidazole-4-c arboxylic acid phenylamide 3 2-(2,4-dichloro-phenyl)-7-hy 4-hydroxy-cyc 0 droxy-1H-benzoimidazole-4-c lohexylamine arboxylic acid 4-hydroxy-cyclohexyl)-amide			arboxylic acid amide				
droxy-1H-benzoimidazole-4-c arboxylic acid phenylamide  3 2-(2,4-dichloro-phenyl)-7-hy 4-hydroxy-cyc 0 droxy-1H-benzoimidazole-4-c lohexylamine arboxylic acid (4-hydroxy-cyclohexyl)-amide	8	က	2-(2,4-dichloro-phenyl)-7-hy		<b>†</b>	6 8.02 (1H, d), 8.01-7.82 (1H, m), 7.81-7.65 (3H.	397
arboxylic acid phenylamide  3 2-(2,4-dichloro-phenyl)-7-hy 4-hydroxy-cyc 0 droxy-1H-benzoimidazole-4-c lohexylamine arboxylic acid (4-hydroxy-cyclohexyl)-amide			droxy-1H-benzoimidazole-4-c	<u> </u>			
3 2-(2,4-dichloro-phenyl)-7-hy 4-hydroxy-cyc 0 droxy-1H-benzoimidazole-4-c lohexylamine arboxylic acid (4-hydroxy-cyclohexyl)-amide			arboxylic acid phenylamide			(H, t), 6.90 (1H, d)	
lohexylamine	~	က	2-(2,4-dichloro-phenyl)-7-hy	<del> </del>	<del> </del>	6 8.02-7.68 (2H, m), 7.68-7.48 (1H, m), 7.20-7.03	419
				lohexylamine			
					-2	2.25-1.85 (4H, m), 1.84-1.39 (4H, m)	···
			(4-hydroxy-cyclohexyl)-amide				

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440	412	427	441
6 7.97 (2H, d), 7.85-7.63 (3H, m), 7.56 (1H, d), 7.38-7.20 (2H, m), 6.82 (1H, d), 3.18 (2H, t), 2.96 (2H, t)	5 8.06-7.81 (4H, m), 7.80-7.64 (1H, s), 7.58 (1H, d), 7.38 (2H, d), 6.84 (1H, d)	5 8.00 (1H, d), 7.98-7.84 (1H, m), 7.75 (1H, m), 7.74-7.52 (2H, m), 7.50-7.26 (1H, m), 7.25-7.05 (2H, m), 7.04-6.80 (1H, m)	8 8.15-7.86 (2H, m), 7.85-7.45 (3H, m), 7.25 (2H, d), 7.20-6.75 (2H, m), 4.58 (1H, t), 3.75 (1H, t), 3.05 (1H, t), 2.81 (1H, t)
0 .	0	0	0
4-aminophenet hylamine	1,4-phenylene diamine	4-aminobenzy alcohol	4-aminophenet hyl alcohol
2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [4-(2-amino- ethyl)-phenyl]-amide	2-(2,4-Dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid (4-amino- phenyl)-amide	2-(2,4-Dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid (4-hydroxy methyl-phenyl)-amide	2-(2,4-Dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [4-(2-hyroxy- ethyl)-phenyl]-amide
m		က	က
24	25	26	27

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droxy-1H-benzoimidazole-4-c o-phenyl)-eth arboxylic acid yl]-4-methyl- {4-[2-(toluene-4-sulfonylami benzensulfona no)-ethyl]-phenyl}-amide mide arboxylic acid yl]-methanesul [4-(2,4-dichloro-phenyl)-7-hy N-[2-(4-amin o droxy-1H-benzoimidazole-4-c o-phenyl)-eth arboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide arboxylic acid ]-isoindole-1, taboxylic acid [-isoindole-1, taboxylic acid ]-isoindole-2-yl)-ethyl]-pheny  1}-amide 3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 6 droxy-1H-benzoimidazole-4-c ulfonic acid [2-(4-amin naboxylic acid [acid [ac	28	3	2-(2,4-dichloro-phenv1)-7-hv	N-[2-(4-amin	-	
arboxylic acid yl]-4-methyl-  {4-[2-(toluene-4-sulfonylami benzensulfona no)-ethyl]-phenyl]-amide mide  3 2-(2,4-dichloro-phenyl)-7-hy N-[2-(4-amin o droxy-1H-benzoimidazole-4-c o-phenyl)-eth arboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  3 2-(2,4-dichloro-phenyl)-7-hy 2-[2-(4-amino o droxy-1H-benzoimidazole-4-c -phenyl)-ethyl arboxylic acid ]-isoindole-2-yl)-ethyl]-pheny  1}-amide  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s o droxy-1H-benzoimidazole-4-c -phenyl)  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s o droxy-1H-benzoimidazole-4-c ulfonic acid[2-(4-amin no-phenyl)-ethyl]-pheny no-phenyl)-ethyl no-phenyl)-ethyl nino)-ethyll-phenyl no-phenyl)-ethyl			droxv-1H-henzoimidazole-1-0			594
arboxylic acid yl]-4-methyl-  {4-[2-(toluene-4-sulfonylami benzensulfona no)-ethyl]-phenyl}-amide mide  3 2-(2,4-dichloro-phenyl)-7-hy N-[2-(4-amin o droxy-1H-benzoimidazole-4-c o-phenyl)-eth arboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  3 2-(2,4-dichloro-phenyl)-7-hy 2-[2-(4-amino o droxy-1H-benzoimidazole-4-c -phenyl)-ethyl arboxylic acid ]-isoindole-2-yl)-ethyl]-pheny  1}-amide  3 2-(2,4-dichloro-phenyl]-pheny l-isoindole-1, thyl)-amide  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s o gdroxy-1H-benzoimidazole-4-c ulfonic acid [2-(4-amin no-phenyl)-ethyl]-pheny no-phenyl)-ethyl no-phenyl)-ethyl					m, 7.38 (2H, d), 7.16 (2H, d), 6.94 (1H, d), 3.10 (2H,	
44-[2-(toluene-4-sulfonylami benzensulfona no)-ethyl]-phenyl}-amide mide  3 2-(2,4-dichloro-phenyl)-7-hy N-[2-(4-amin 0 droxy-1H-benzoimidazole-4-c o-phenyl)-eth arboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  3 2-(2,4-dichloro-phenyl)-7-hy 2-[2-(4-amino 0 droxy-1H-benzoimidazole-4-c -phenyl)-ethyl arboxylic acid ]-isoindole-1, {4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny l}-amide  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 6 droxy-1H-benzoimidazole-4-c ulfonic acid[2-(4-ami n n-phenyl)-eth n no-phenyl)-eth				yl]-4-methyl-	t), 2.73 (2H, t), 2.43 (3H, s)	
arboxylic acid J-phenyl]—phenyl]—phenyl]—amide mide  3 2-(2,4-dichloro-phenyl)-7-hy M-[2-(4-amin 0 droxy-1H-benzoimidazole-4-c o-phenyl)-eth arboxylic acid yl]-methanesul futyl)-phenyl]—amide thyl)-phenyl]—amide acid J-isoindole-1, {4-[2-(4-amin 0 droxy-1H-benzoimidazole-4-c phenyl)-ethyl arboxylic acid J-isoindole-1, {4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny l}-amide 3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 6 droxy-1H-benzoimidazole-4-c ulfonic acid acid[2-(4-amin namino)-athyl]-pheny acid acid[2-(4-amin namino)-athyl]-acid acid acid[2-(4-amin namino)-athyl]-acid acid acid[2-(4-amin namino)-athyl]-acid acid acid acid acid acid acid acid			{4-[2-(toluene-4-sulfonylami	benzensulfona		
3 2-(2,4-dichloro-phenyl)-7-hy N-[2-(4-amin of droxy-1H-benzoimidazole-4-c o-phenyl)-eth arboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  3 2-(2,4-dichloro-phenyl)-7-hy 2-[2-(4-amino of droxy-1H-benzoimidazole-4-c phenyl)-ethyl arboxylic acid ]-isoindole-1, {4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny l}-amide  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s of droxy-1H-benzoimidazole-4-c ulfonic acid[2-(4-amin numb)-athyl]-pheny acid acid[2-(4-amin numb)-athyl]-behyl]-b			no)-ethyl]-phenyl}-amide	mide		
droxy-1H-benzoimidazole-4-c o-phenyl)-eth arboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  3 2-(2,4-dichloro-phenyl)-7-hy 2-[2-(4-amino 0 droxy-1H-benzoimidazole-4-c -phenyl)-ethyl arboxylic acid ]-isoindole-1, [4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny l}-amide  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 6 droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid [2-(4-ami nn-2-thyl]-phenyl]-eth	53	က	2-(2,4-dichloro-phenyl)-7-hy	†	6 8.02 (1H, d). 8.01-7.78 (1H m) 7.70 (9H d)	518
arboxylic acid yl]-methanesul [4-(2-methanesul fonamioe fonamide thyl)-phenyl]-amide  3 2-(2,4-dichloro-phenyl)-7-hy 2-[2-(4-amino of droxy-1H-benzoimidazole-4-c -phenyl)-ethyl arboxylic acid ]-isoindole-1, {4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny l}-amide  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s of droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid [2-(4-ami nn floor)-ethyl]-pheny acid acid[2-(4-ami nn floor)-ethyl]-phenyl no-phenyl)-eth			droxy-1H-benzoimidazole-4-c	o-phenyl)-eth		010
[4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  3 2-(2,4-dichloro-phenyl)-7-hy 2-[2-(4-amino 0 droxy-1H-benzoimidazole-4-c -phenyl)-ethyl arboxylic acid ]-isoindole-1, {4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny l}-amide  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid[2-(4-ami 1-hygylic)-ethyl]-phenyl]-acid acid[2-(4-ami 1-hygylic)-ethyl]-acid acid[2-(4-ami 1-hygylic)-ethylloro-ethylloro-ethylloro-ethylloro-ethylloro-ethylloro-ethylloro-ethylloro-ethyllor				yl]-methanesul	(2H, t), 2.84 (2H, t), 2.82 (3H.s)	
thyl)-phenyl]-amide  3			[4-(2-methanesulfonylamino-e			
3 2-(2,4-dichloro-phenyl)-7-hy 2-[2-(4-amino 0 droxy-1H-benzoimidazole-4-c -phenyl)-ethyl arboxylic acid ]-isoindole-1, {4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny   1}-amide 3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid [2-(4-ami no-phenyl)-ethyl]-bethyll-chemillosis   4-[2-(thiophene-2-sulfonyla no-phenyl)-ethyll-chemillosis   4-[2-(thiophene-2-sulfonyla no-phenyl]-chemillosis   4-[2-(thiophene-2-sulfonyla no-phenyl]-chemillosis   4-[2-(thiophene-2-sulfonyla no-phenyl]-chemillosis   4-[2-(thiophene-2-sulfonyla no-phenyl]-chemillosis   4-[2-(thiophene-2-sulfonyla no-phenyla n			thyl)-phenyl]-amide			
droxy-1H-benzoimidazole-4-c -phenyl)-ethyl arboxylic acid l-isoindole-1, {4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny l}-amide 3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s of droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid[2-(4-ami arboxylic acid[2-(4-ami mino)-ethyl]-chanillarian no-phenyl)-eth	30	က	2-(2,4-dichloro-phenyl)-7-hy	+	8 7.10 (1H, d), 6.99-6.81 (6H, m), 6.80-6.65 (3H	570
arboxylic acid ]-isoindole-1,  {4-[2-(1,3-dioxo-1,3-dihydro 3-dione -isoindole-2-yl)-ethyl]-pheny  l}-amide  3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0  droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid[2-(4-ami acid 2-(thiophene-2-sulfonyla no-phenyl)-eth			droxy-1H-benzoimidazole-4-c	-phenyl)-ethyl		5
[4-[2-(1,3-dioxo-1,3-dihydro]] 3-dione lisoindole-2-yl]-ethyl]-pheny l}-amide 3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid[2-(4-ami)] [4-[2-(thiophene-2-sulfonyla]] 1				]-isoindole-1,	t)	
-isoindole-2-yl)-ethyl]-pheny  1}-amide  3    2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid [2-(4-ami) 4-[2-(thiophene-2-sulfonyla no-phenyl)-eth			{4-[2-(1,3-dioxo-1,3-dihydro	3-dione		
1}-amide  3			-isoindole-2-yl)-ethyl]-pheny			
3 2-(2,4-dichloro-phenyl)-7-hy thiophene-2-s 0 droxy-1H-benzoimidazole-4-c ulfonic arboxylic acid [2-(4-ami 4-[2-(thiophene-2-sulfonyla no-phenyl)-eth mino)-ethyll-phonyllomidation		į	1}-amide			
-c ulfonic sid acid[2-(4-ami a no-phenyl)-eth	31	က	2-(2,4-dichloro-phenyl)-7-hy	<del>                                     </del>	8 8.08 (1H, d), 7.88 (2H, m). 7.83 (1H, d) 7.75 (1H, 5	586
a no-phenyl)-eth		_	droxy-1H-benzoimidazole-4-c	ulfonic		2
a no-phenyl)-eth				acid[2-(4-ami	m), 6.97 (1H, d), 3.16 (2H. t). 2.77 (2H t)	
			{4-[2-(thiophene-2-sulfonyla	no-phenyl)-eth		
_			mino)-ethyl]-phenyl}-amide	yl]-amide		

2-(2,4-dich		N-[2-(4-amin	0	6 8.11 (1H, d), 7.95-7.82 (2H, m), 7.75-7.60 (3H,
drioxy-1H-benzoimidazole-4-	zole-4-	o-phenyl)-eth		m), 7.28 (2H, d), 7.01 (1H, d), 3.31 (2H, t), 2.98 (2H,
carboxylic acid [4-(2-		yl]-ethanesulf		q), 2.85 (2H, t), 1.24 (3H, t)
ethanesulfonylamino-ethyl)-ph		onamide		
enyl]-amide			_	
2-(4-fluoro-phenyl)-7-hydrox		N-[2-(4-amin	0	6 8.23-8.15 (2H, m), 7.91 (1H, d), 7.69 (2H, d), 7.39
y-1H-benzoimidazole-4-carbo		o-phenyl)-eth		(2H, t), 7.26 (2H, d), 6.83 (1H, d), 3.31 (2H. t).
xylic acid [4-(2-methane		yl]-methanesul	<del></del>	2.85-2.78 (5H, m)
sulfonylamino-ethyl)-phenyl]-		fonamide		
amide				
2-(4-fluoro-phenyl)-7-hydrox		N-[2-(4-amin (	0	8 8.25-8.21 (2H, m), 7.98-7.93 (2H, m) 7.71-7 64
y-1H-benzoimidazole-4-carbo	<u> </u>	o-phenyl)-eth		(4H, m), 7.41–7.34 (3H, m), 7.14 (2H, d), 6.87 (1H)
xylic acid {4-[2-		yl]-4-methyl-	_ <u>_</u>	d), 3.08 (2H, t), 2.73 (2H, t), 2.40 (3H, s)
(toluene-4-sulfonylamino)-eth		benzensulfona		
yl]-phenyl}-amide	_ <del>E</del>	mide	<del></del>	
2-(4-fluoro-phenyl)-7-hydrox		N-[2-(4-amin 0	<del>                                     </del>	6 8.05 (2H, t), 7.78 (1H, d), 7.30 (2H, t), 7.14 (2H, d).
y-1H-benzoimidazole-4-carbo		o-phenyl)-eth		6.77 (2H, d), 6.69 (1H, d), 3.78 (2H, q), 3.35 (2H, t)
xylic acid [4-(	2-	yl]-ethanesulf		2.90 (2H, t), 1.28 (3H, t)
methanesulfonylamino-ethyl)		onamide		
phenyl]-amide	<del></del> .			

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y-1H-benzoimidazole-4-carbo xylic acid (4-morpholin-4- ne yl-phenyl)-amide  7	36	4	2-(4-fluoro-phenyl)-7-hydrox	4-mornholin-4	C	
xylic acid (4-morpholin-4- ne yl-phenyl)-amide  2-(2,4-difluoro-phenyl)-7-hyd			y-1H-benzoimidazole-4-carbo		>	
yl-phenyl)-amide  2 -(2,4-difluoro-phenyl)-7-hyd   N-[2-(4-amin   0 roxy-1H-benzoimidazole-4-ca   o-phenyl)-eth rboxylic   acid   [4-(2- yl]-methanesul methanesulfonylamino-ethyl)-  fonamide   phenyl]-amide   phenyl]-amide   roxy-1H-benzoimidazole-4-ca   o-phenyl)-eth rboxylic   acid   [4-[2-(toluene yl]-4-methyl-4-sulfonylamino)-ethyl]-phe   penzensulfona   mide   phenyl]amide   mide   carboxylic   acid   [4-(2-methane yl]-eth roxy-1H-benzoimidazole-4-   o-phenyl)-eth   carboxylic   acid   [4-(2-methane yl]-ethanesulf   tanide   sulfonylamino-ethyl]-phenyl]-   onamide   amide   acid   amide   amide   amide   acid   amide   acid   amide   acid   acid			xylic acid (4-morpholin-4-			
5 2-(2,4-difluoro-phenyl)-7-hyd			yl-phenyl)-amide			
roxy-1H-benzoimidazole-4-ca o-phenyl)-eth rboxylic acid [4-(2- yl]-methanesul methanesulfonylamino-ethyl)- fonamide phenyl]-amide  2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin orvoy-1H-benzoimidazole-4-ca o-phenyl)-eth rboxylic acid (4-[2-(toluene yl]-4-methyl-4-sulfonylamino)-ethyl]-phe benzensulfona nyl}amide  5 2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin orvoy-1H-benzoimidazole-4- o-phenyl)-eth carboxylic acid [4-(2-methane yl]-ethanesulf tanide sulfonylamino-ethyl)-phenyl]- onamide amide	37	വ	2-(2,4-difluoro-phenyl)-7-hyd	N-[2-(4-amin	0	6 7.90 (1H, d), 7.62 (1H, d), 7.31–7.17 (4H, m), 6.81
rboxylic acid [4-(2- yl]-methanesul methanesulfonylamino-ethyl)- fonamide phenyl]-amide  5			roxy-1H-benzoimidazole-4-ca			(1H, d), 3.22 (2H, t), 2.76 (5H,m)
methanesulfonylamino-ethyl)- fonamide phenyl]-amide  5			acid	yl]-methanesul		
phenyl]-amide  2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin orxy-1H-benzoimidazole-4-ca o-phenyl)-eth rboxylic acid {4-[2-(toluene yl]-4-methyl-4-sulfonylamino)-ethyl]-phe benzensulfona mide  5 2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin orxy-1H-benzoimidazole-4-o-phenyl)-eth carboxylic acid [4-(2-methane yl]-ethanesulf sulfonylamino-ethyl)-phenyl]- onamide  amide			methanesulfonylamino-ethyl)-	fonamide		
roxy-1H-benzoimidazole-4-ca o-phenyl)-eth rboxylic acid {4-[2-(toluene yl]-4-methyl-4-sulfonylamino)-ethyl]-phe benzensulfona nyl}amide mide mide carboxylic acid [4-(2-methane yl]-tethanesulf carboxylic acid [4-(2-methane yl]-ethanesulf sulfonylamino-ethyl)-phenyl]- onamide amide amide amide			phenyl]-amide			
roxy-1H-benzoimidazole-4-ca o-phenyl)-eth rboxylic acid {4-[2-(toluene yl]-4-methyl4-sulfonylamino)-ethyl]-phe benzensulfona nyl}amide mide  5 2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin 0 roxy-1H-benzoimidazole-4- o-phenyl)-eth carboxylic acid [4-(2-methane yl]-ethanesulf sulfonylamino-ethyl)-phenyl]- onamide amide	38	2	2-(2,4-difluoro-phenyl)-7-hyd	N-[2-(4-amin	+-	8 7.99 (1H, m), 7.74 (1H, d), 7.50 (2H, d). 7.33-7.26
rboxylic acid {4-[2-(toluene yl]-4-methyl4-sulfonylamino)-ethyl]-phe benzensulfona nyl}amide mide  5 2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin 0 arboxylic acid [4-(2-methane yl]-ethanesulf sulfonylamino-ethyl)-phenyl]- onamide amide			roxy-1H-benzoimidazole-4-ca			(2H, m), 7.23 (4H, m), 6.94 (2H, d), 6.81 (1H, d), 3.58
-4-sulfonylamino)-ethyl]-phe benzensulfona nyl}amide  5 2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin 0 roxy-1H-benzoimidazole-4- o-phenyl)-eth carboxylic acid [4-(2-methane yl]-ethanesulf sulfonylamino-ethyl)-phenyl]- onamide amide			rboxylic acid (4-[2-(toluene		<u> </u>	(2H, t), 2.82 (2H, t), 2.23 (3H, s)
nyl}amide mide  5 2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin 0 roxy-1H-benzoimidazole-4- o-phenyl)-eth carboxylic acid [4-(2-methane yl]-ethanesulf sulfonylamino-ethyl)-phenyl]- onamide amide			-4-sulfonylamino)-ethyl]-phe	benzensulfona		
5 2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin 0 roxy-1H-benzoimidazole-4- o-phenyl)-eth carboxylic acid [4-(2-methane yl]-ethanesulf sulfonylamino-ethyl)-phenyl]- onamide amide	-		nyl}amide	mide		
1H-benzoimidazole-4- o-phenyl)-eth  tylic acid [4-(2-methane yl]-ethanesulf  ylamino-ethyl)-phenyl]- onamide	39	5				\$ 8.19-8.00 (2H, m), 7.70 (1H, d), 7.43-7.26 (4H.
<pre>xylic acid [4-(2-methane   yl]-ethanesulf ylamino-ethyl)-phenyl]-   onamide</pre>			roxy-1H-benzoimidazole-4-	o-phenyl)-eth	——	n), 6.87 (1H, d), 3.98 (2H, t), 2.97 (2H. q), 2.86 (2H
ylamino-ethyl)-phenyl]-					<u> </u>	), 1.25 (3H, t)
amide				onamide		
			amide			

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6 8.01-7.93 (1H, m), 7.65 (3H, t), 7.53-7.44 (2H, m), 7.33 (4H, m), 7.11 (2H, d), 6.80 (1H, d), 3.09 (2H, t), 2.72 (2H, t), 2.38 (3H, s)	8 8.06 (1H, m), 7.97 (1H, d), 7.68-7.61 (3H, m), 7.40 (1H, m), 7.27 (2H, m), 6.97 (1H, m), 3.61 (2H, t), 2.84 (5H, m)	5 8.07 (1H, m), 7.97 (1H, d), 7.68-7.40 (3H, m), 7.28-7.18 (3H, m), 6.99 (1H, d), 3.61 (2H, t), 2.96 (2H, q), 2.84 (2H, t), 1.28 (3H, t)
0	0	0
N-[2-(4-amin o-phenyl)-eth yl]-4-methyl-benzensulfona mide)	N-[2-(4-amin o-phenyl)-eth yl]-methanesul fonamide	N-[2-(4-amin o-phenyl)-eth yl]ethanesulfon amide
2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid {4-[2-(toluene-4-sulfonylamino)-ethyl]-phenyl}amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [4-(2-methanesulfonylamino-ethyl)-phenyl]-amide	2-(2-chloro-4-fluoro-phenyl) N-[2-(4-amin -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid [4-(2- yl]ethanesulformethanesulfonylamino-ethyl)- amide phenyl]-amide
9	9	9
40	41	42

1.2   2-3-chloro-4-fluoro-pheny    N-[2-(4-amin of phenyl)   N-[2-(4	ç	t		$\vdash$			ļ
-7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-4-methyl- {4-[2-(toluene-4-sulfonylami benzensulfona no)-ethyl]-phenyl}amide mide -7 2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin o -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-ethanesulf thyl)-phenyl]-amide thyl)-phenyl]-amide acid yl]-methanesulf yl]-methanesulf yl]-methanesulf yl]-methanesulf thyl)-phenyl]-amide fonamide thyl)-phenyl]-amide 1 cyclohexyl-(7-hydroxy-2-phe piperidine 0 6 nyl-1H-benzoimidazole-4-yl)-methanone 2 2-(4-chloro-phenyl)-7-hydro piperidine 0 6 xy-1H-benzoimidazole-4-carb					0	8 8.18 (1H, d), 7.90 (1H, m), 7.72 (1H, d), 7.47 (2H.	_
e-4-carboxylic acid yl]-4-methyl- {4-[2-(toluene-4-sulfonylami benzensulfona no)-ethyl]-phenyl}amide mide no)-ethyl]-phenyl}amide mide  -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-ethanesulf thyl)-phenyl]-amide onamide thyl)-phenyl]-amide  -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine 0 6 nyl-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro oxylic acid cyclohexyl-amide oxylic acid cyclohexyl-amide			-7-hydroxy-1H-benzoimidazo			d), 7.39 (1H, m), 7.13-7.06 (4H, m), 6.95(2H, d)	
44-[2-(toluene-4-sulfonylami benzensulfona no)-ethyl]-phenyl}amide mide  7 2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin 0 -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-ethanesulf [4-(2-methanesulfonylamino-e onamide thyl)-phenyl]-amide  7 2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin o -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine o syl-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro piperidine o xyl-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide				l yl]-4-methyl-		6.75 (1H, d), 3.63 (2H, t), 2.85 (2H, t), 2.23 (3H s)	
no)-ethyl]-phenyl}amide mide  2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin 0 -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-ethanesulf [4-(2-methanesulfonylamino-e onamide thyl)-phenyl]-amide thyl)-phenyl]-amide o-7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide oxyli-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro piperidine o xylic acid cyclohexyl-amide oxylic acid cyclohexyl-amide			4-[2-(toluene-4-sulfonylami	benzensulfona			
2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin of a-f-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-ethanesulf [4-(2-methanesulfonylamino-e onamide thyl)-phenyl]-amide onamide acid yl]-methanesull (4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide acid yl]-methanesull [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide thyl)-phenyl]-amide orphenyl]-amide acid cyclohexyl-(7-hydroxy-2-phe piperidine of myl-1H-benzoimidazole-4-yl)- methanone acid cyclohexyl-7-hydro piperidine ocylic acid cyclohexyl-amide oxylic acid cyclohexyl-amide		_	no)-ethyl]-phenyl}amide	mide			·
-7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-ethanesulf [4-(2-methanesulfonylamino-e onamide thyl)-phenyl]-amide -7 2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin o -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine o nyl-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide	44		2-(3-chloro-4-fluoro-phenyl)	†—	<del> </del>	6 8.27 (1H, d), 8.10 (1H, m). 7.85 (1H, d) 7.64 (2H	
e-4-carboxylic acid yl]-ethanesulf [4-(2-methanesulfonylamino-e onamide thyl)-phenyl]-amide  7 2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin 0 -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine 0 finathanone		<del></del>	-7-hydroxy-1H-benzoimidazo			d), 7.41 (1H, t), 7.22 (2H, d), 6.76 (1H, d), 3.26 (2H	
[4-(2-methanesulfonylamino-e thyl)-phenyl]-amide thyl)-phenyl]-amide  7 2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin 0 -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine onyl-1H-benzoimidazole-4-yl)- methanone 2 2-(4-chloro-phenyl)-7-hydro piperidine oxylic acid cyclohexyl-amide					<u> </u>	t), 2.94 (2H, q), 2.80 (2H, t), 1.22(3H, t)	
thyl)-phenyl]-amide  2-(3-chloro-4-fluoro-phenyl)			[4-(2-methanesulfonylamino-e				
7 2-(3-chloro-4-fluoro-phenyl) N-[2-(4-amin 0 -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide cyclohexyl-(7-hydroxy-2-phe piperidine 0 nyl-1H-benzoimidazole-4-yl)-methanone zy-(4-chloro-phenyl)-7-hydro piperidine 0 xy-1H-benzoimidazole-4-carb cyclohexyl-amide oxylic acid cyclohexyl-amide			thyl)-phenyl]-amide				
-7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine 0 nyl-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro piperidine 0 xy-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide	45	7	2-(3-chloro-4-fluoro-phenyl)	$\vdash$	<del>                                     </del>	5 8.31 (1H, d), 8.12 (1H, m), 7.91 (1H, d), 7.68 (2H	
e-4-carboxylic acid yl]-methanesul [4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine 0 nyl-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro piperidine 0 xy-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide		<del></del>	-7-hydroxy-1H-benzoimidazol	_		1), 7.47 (1H, t), 7.26 (2H, d), 6.83 (1H, d), 3.31 (2H	
[4-(2-methanesulfonylamino-e fonamide thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine 0 nyl-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro piperidine 0 xy-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide						), 2.85 (5H, m)	
thyl)-phenyl]-amide  1 cyclohexyl-(7-hydroxy-2-phe piperidine 0  nyl-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro piperidine 0  xy-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide			[4-(2-methanesulfonylamino-e	fonamide			
1 cyclohexyl-(7-hydroxy-2-phe piperidine 0 nyl-1H-benzoimidazole-4-yl)- methanone  2 2-(4-chloro-phenyl)-7-hydro piperidine 0 xy-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide		_	thyl)-phenyl]-amide				
nyl-1H-benzoimidazole-4-yl)- methanone  2	46	-	cyclohexyl-(7-hydroxy-2-phe				320
2 2-(4-chloro-phenyl)-7-hydro piperidine 0 xy-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide			nyl-1H-benzoimidazole-4-yl)-		(1)		
2 2-(4-chloro-phenyl)-7-hydro piperidine 0 xy-1H-benzoimidazole-4-carb oxylic acid cyclohexyl-amide		_	methanone				
q	47	2	2-(4-chloro-phenyl)-7-hydro		_		355
			xy-1H-benzoimidazole-4-carb		<del>-</del>		) ) )
			oxylic acid cyclohexyl-amide				

2-(2,4-	2-(2,4-dichloro-phenyl)-7-hy	piperidine	0	8 7.31-7.23 (3H, m), 7.05 (1H, d), 6.64 (1H, d)	389
droxy-1H-b	droxy-1H-benzoimidazole-4-y			3.53-3.29 (4H, m), 1.82-1.41 (6H, m)	
-piperidine	1-piperidine-1-y1-methanone	-			
7-hydroxy	7-hydroxy-2-phenyl-1H-benz	4-nitrobenzyla		8 8.20 (2H, d), 8.13 (2H, d), 7.82 (1H, d), 7.82-7.55	388
oimidazole	oimidazole-4-carboxylic	mine-hydrochl		(5H, m), 6.87 (1H, d), 4.75 (2H, s)	 }
ıcid(4-ni	acid(4-nitro-benzyl)-amide	oride)			
'-hydrox	7-hydroxy-2-phenyl-1H-benz	4-aminobenzyl		8 8.15 (2H, d), 7.82 (1H, d), 7.72-7.52 (5H, m), 7.33	358
imidazol	oimidazole-4-carboxylic acid	amine-dihydro		(2H, d), 6.87 (1H, d), 4.70 (2H, s)	
4-amino	(4-amino-benzyl)-amide	chloride			
-hydro	7-hydroxy-2-phenyl-1H-benz	benzylamine	1	8 8.10 (2H, d), 7.87 (1H, d), 7.85-7.60 (3H, m), 7.40	343
imidazo	oimidazole-4-carboxylic acid			(2H, d), 7.39-7.28 (2H, m), 7.27-7.20 (1H, m), 6.89	
benzylamide	nide			(1H, d), 4.66 (2H, s)	
-(4-ch	2-(4-chloro-phenyl)-7-hydro	benzylamine	н	8 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 7.42-7.23	377
y-1H-t	xy-1H-benzoimidazole-4-carb				
xylic ac	oxylic acid benzylamide				
-(4-chl	2-(4-chloro-phenyl)-7-hydro	4-nitrobenzyla	-	12 8 20 (5 H1) 88 2 (F H6) 00 2 (F H6) 08 8	8
к-1Н-Ъ	xx-1H-benzoimidazole-4-carb	mine-hydrochl			774
xylic aci	oxylic acid(4-nitro-benzyl)-	oride			-
amide					

xy-1H-benzoimidazole-4-carb amine-hydroxy oxylic acid (4-amino-benzyl)- chloride amide  3 2-(2,4-dichloro-phenyl)-7-hy benzylamine droxy-1H-benzoimidazole-4-c mine arboxylic acid benzylamide  3 2-(2,4-Dichloro-phenyl)-7-hy 4-nitrobenzyla chroxy-1H-benzoimidazole-4-c mine arboxylic acid benzylamide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin oimidazole-4-carboxylic acid ethylamine dimidazole-4-carboxylic acid ethylamine  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 oimidazole-4-carboxylic acid ethylamine  (4-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide  1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide	54	6	9-(4-chloro-chorum) 7 1-13-1		<u>_</u> ,		
xy-1H-benzoimidazole-4-carb amine-hydroxy oxylic acid (4-amino-benzyl)- chloride amide  3 2-(2,4-dichloro-phenyl)-7-hy benzylamine l droxy-1H-benzoimidazole-4-c arboxylic acid benzylamide droxy-1H-benzoimidazole-4-c mine arboxylic acid benzyl)-amide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 doimidazole-4-carboxylic acid ethylamine 2 doimidazole-4-carboxylic acid ethylamine 2 doimidazole-4-carboxylic acid ethylamine 3 doimidazole-4-carboxylic acid ethylamine 4-hydroxy-2-phenyl-1H-benz dethyl)-amid 6 e doimidazole-4-carboxylic acid ethylamine 1 7-hydroxy-2-phenyl-1H-benz doimidazole-4-carboxylic acid ethylamine 1 7-hydroxy-2-phenyl-1H-benz doimidazole-4-carboxylic acid ethylamine 1 7-hydroxy-2-phenyl-1H-benz doimidazole-4-carboxylic acid dethylamine 1 7-hydroxy-2-phenyl-1H-benz doimidazole-4-carboxylic acid dethylamine 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenylic acid dethylamine 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenyl)-amide 1 7-hydroxy-2-phenyllic acid dethylamine 1 7-hydroxy-2-phenyllic acid dethyllic acid dethylamine 1 7-hydroxy-2-phenyllic acid dethyllic acid dethy	5	<u> </u>	z (* cinolo-pileliyi)-/-nyaro	4-aminobenzyl	_	8 8.20 (2H, d), 7.90 (2H, d), 7.88 (1H, s), 7.69-7.51	392
oxylic acid (4-amino-benzyl)- chloride  amide  3 2-(2,4-dichloro-phenyl)-7-hy benzylamine 1 droxy-1H-benzoimidazole-4-c arboxylic acid benzylamide droxy-1H-benzoimidazole-4-c arboxylic acid benzylamide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 doimidazole-4-carboxylic acid ethylamine 2 doimidazole-4-carboxylic acid ylamine 2 doimidazole-4-carboxylic acid ylamine 2 doimidazole-4-carboxylic acid ylamine 2 definitro-phenethyl)-amide 2 definitro-phenethyl)-amide 3 definite 3			xy-1H-benzoimidazole-4-carb			(4H, m), 6.91 (1H, d), 4.76 (2H, s)	
amide  3 2-(2,4-dichloro-phenyl)-7-hy benzylamine 1 droxy-1H-benzoimidazole-4-c arboxylic acid benzylamide  4 2-(2,4-Dichloro-phenyl)-7-hy 4-nitrobenzyla 1 droxy-1H-benzoimidazole-4-c mine arboxylic acid benzyl-amide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 6 -phenethyl-amide  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 6 oimidazole-4-carboxylic acid ethylamine (4-hydroxy-2-phenyl-1H-benz 4-hydroxyphenethyl)-amid e  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 6 oimidazole-4-carboxylic acid ethylamine 6 6 1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 8 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide	<del></del>	·	oxylic acid (4-amino-benzyl)-	chloride			
droxy-1H-benzoimidazole-4-c arboxylic acid benzylamide  3 2-(2,4-Dichloro-phenyl)-7-hy 4-nitrobenzyla 1 droxy-1H-benzoimidazole-4-c mine arboxylic acid benzylamide  4-nitro-benzyl)-amide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 doimidazole-4-carboxylic acid e -phenethyl-amide  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 doimidazole-4-carboxylic acid ethylamine (4-hydroxy-2-phenyl-1H-benz 4-hydroxyphenethyl)-amid e  1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 doimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide			amide				
droxy-1H-benzoimidazole-4-c arboxylic acid benzylamide  3 2-(2,4-Dichloro-phenyl)-7-hy 4-nitrobenzyla 1 droxy-1H-benzoimidazole-4-c arboxylic acid (4-nitro-benzyl)-amide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 doimidazole-4-carboxylic acid e -phenethyl-amide  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 doimidazole-4-carboxylic acid ethylamine  2 4-hydroxy-2-phenyl-1H-benz 4-hitropheneth 2 doimidazole-4-carboxylic acid ylamine  3 4-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 doimidazole-4-carboxylic acid ylamine  4 -hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 doimidazole-4-carboxylic acid ylamine  (4-nitro-phenethyl)-amide	55	က	2-(2,4-dichloro-phenyl)-7-hy	benzylamine	1		411
arboxylic acid benzylamide  3			droxy-1H-benzoimidazole-4-c				1 1 1
droxy-1H-benzoimidazole-4-c mine arboxylic acid (4-nitro-benzyl)-amide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 oimidazole-4-carboxylic acid e -phenethyl-amide  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 oimidazole-4-carboxylic acid ethylamine (4-hydroxy-2-phenyl)-amid e (4-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 6 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide			arboxylic acid benzylamide				
droxy-1H-benzoimidazole-4-c mine arboxylic acid (4-nitro-benzyl)-amide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 oimidazole-4-carboxylic acid e -phenethyl-amide  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 oimidazole-4-carboxylic acid ethylamine (4-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 6 oimidazole-4-carboxylic acid ylamine oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide	26	က	2-(2,4-Dichloro-phenyl)-7-hy	4-nitrobenzyla		<del></del>	456
arboxylic acid  (4-nitro-benzyl)-amide  1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2  oimidazole-4-carboxylic acid e  -phenethyl-amide  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2  oimidazole-4-carboxylic acid ethylamine  (4-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2  oimidazole-4-carboxylic acid ylamine  (4-nitro-phenethyl)-amide			droxy-1H-benzoimidazole-4-c	mine			2
1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 oimidazole-4-carboxylic acid e -phenethyl-amide 1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 oimidazole-4-carboxylic acid ethylamine (4-hydroxy-2-phenyl)-amid e 1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 acid oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide							
1 7-hydroxy-2-phenyl-1H-benz phenethylamin 2 oimidazole-4-carboxylic acid e -phenethyl-amide 1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 oimidazole-4-carboxylic acid ethylamine (4-hydroxy-pheneethyl)-amid e 1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 acid oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide			(4-nitro-benzyl)-amide				
oimidazole-4-carboxylic acid e  -phenethyl-amide  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 oimidazole-4-carboxylic acid ethylamine (4-hydroxy-2-phenyl)-amid  1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 acid oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide	22	~	7-hydroxy-2-phenyl-1H-benz		2		357
-phenethyl-amide  1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 oimidazole-4-carboxylic acid ethylamine (4-hydroxy-pheneethyl)-amid e  1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 6 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide				Ð			• >
1 7-hydroxy-2-phenyl-1H-benz 4-hydroxyphen 2 oimidazole-4-carboxylic acid ethylamine (4-hydroxy-pheneethyl)-amid e  1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide			phenethyl-amide			(2H, t)	
oimidazole-4-carboxylic acid ethylamine (4-hydroxy-pheneethyl)-amid  e  1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide	28		7-hydroxy-2-phenyl-1H-benz	<del> </del>	$\vdash$	-7.92 (2H, m), 7.77 (1H, d), 7.62-7.42 (3H)	373
(4-hydroxy-pheneethyl)-amid  e  1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide				ethylamine			
1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide			(4-hydroxy-pheneethyl)-amid			t), 2.83 (2H, t)	
1 7-hydroxy-2-phenyl-1H-benz 4-nitropheneth 2 oimidazole-4-carboxylic acid ylamine (4-nitro-phenethyl)-amide			υ				
acid ylamine	59		<del> </del> -	<del> </del>	1		402
			acid	ylamine			]
			(4-nitro-phenethyl)-amide			2H, t)	

,	_			ľ		
09		7-hydroxy-2-phenyl-1H-benz oimidazole-4-carboxylic acid (4-amino-phenethyl)-amino	4-aminophenet hylamine	8	5 8.11 (2H, d), 7.78 (1H, d), 7.74-7.59 (3H, m), 7.46 (2H, d), 7.31 (2H, d), 6.85 (1H, d), 3.72 (2H, t), 3.02 (2H, t)	372
61	н	7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylicacid (2-amino-ethyl)-amide	ethylenediamin 8	2	6 7.95-7.70 (2H, m), 7.69 (1H, d), 7.60-7.42 (1H, m), 7.41-7.23 (2H, m), 3.77 (2H, t), 3.25 (2H, t)	296
62	1	7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylicacid (4-hydroxy-3-methoxy-phenethyl)-amide	4-hydroxy-3- 2 methoxyphenet hylamine	2	δ 8.10-8.00 (2H, m), 7.78 (1H, d), 7.69-7.52 (3H, m), 6.91-6.77 (2H, m), 6.72 (2H, d), 3.73 (3H, s), 3.70 (2H, t), 2.89 (2H, t)	403
63		7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylicacid (3-hydroxy-4-methoxy-phenethyl)-amide	3-hydroxy-4- 2 methoxyphenet hylamine	<del> </del>	\$ 8.08-7.93 (2H, m), 7.78 (1H, d), 7.62-7.50 (2H, m), 6.98-6.52 (5H, m), 3.80 (3H, s), 3.68 (2H, t), 2.82 (2H, t)	403
64	H	7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylicacid[2-(4-methanesulfonylamino-phenyl)-ethyl]-amide	N-[4-(2-amin 2 o-ethyl)-phen yl]-methanesul fonamide	<del></del>	5 8.07 (1H, d), 7.77 (1H, d), 7.65-7.61 (4H, m), 7.28 (2H, d), 7.18 (2H, d), 6.85 (1H, d), 3.71 (2H, t), 2.95 (2H, t), 2.85 (3H, s)	450

	_					
- 65	-	7-hydroxy-2-phenyl-1H-	N-[4-(2-amin	2	8 8.09 (2H, d), 7.76-7.54 (5H m) 7 33-7 30 (3H	526
		benzoimidazole-4-carboxylic	o-ethyl)-phen		m), 7.20–7.13 (2H. m), 7.01–6.87 (3H. m), 3.73 (1H.	020
		acid{2-[4-(toluene-4-sulfonyl	yl]-4-methyl-		t), 3.63 (1H. t). 3.01 (1H. t). 2.88 (1H. t). 9.44 (3H. c).	
<del></del> _		amino)-phenyl]-ethyl}-amide	benzensulfona		(0, 110, 51, 51, 50, 51, 51, 51, 51, 51, 51, 51, 51, 51, 51	
	_		mide			_
99		7-hydroxy-2-phenyl-H-benzo	4-(2-aminoeth	2	6 8.17-8.12 (2H m) 788 (1H d) 777-71 (211	200
		imidazole-4-carboxylic acid	acid yl) morpholine			200
		(2-morpholin-4-yl-ethyl)-ami		<del></del>	t), 3.47 (2H, t), 3.46-3.00 (4H, t)	
		de				
29	-	7-hydroxy-2-phenyl-1H-benz	2-[4-(2-amino 2	2 8	6 8.14 (2H, d). 7.97-7.68 (8H m) 7.40 (4H da)	6
		oimidazole-4-carboxylic	-ethyl)-phenyl		6.93 (1H, d), 3.74 (2H, †) 3.05 (7H, †)	700
		acid{2-[4-(1,3-dioxo-1,3-dih	]-isoindole-1,		() (TT) () () (() (TT) () () () () () () () () () () () () ()	
		ydro-isoindole-2-yl)-phenyl]-	3-dione			=
		ethyl}-amide				
89	Н	7-hydroxy- $2$ -phenyl- $1$ H-benz $N$ - $[4$ - $(2$ -amin	N-[4-(2-amin 2	_	6 8.15 (2H, d), 7.79-7.72 (4H m) 7.99 (4H dd)	
		oimidazole-4-carboxylic acid	acid o-ethyl)-phen	<u> </u>	6.97 (1H, d). 3.66 (2H, f). 2.99 (2H, g). 2.89 (3H, c).	
		[2-(4-ethanesulfonylamino-ph	yl]-ethansulfo	_ <u></u>	1.22 (3H, t)	
		enyl)-ethyl]-amide	namide			
						_

70 1	oimidazole-4-carboxylic acid			。 ここう ( でこ ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( )	2
		ylamino)-5-nit			418
	(5-mitropyridine-2-amino-eth	ropyridine		(III (111) 00:0 Table (2) (2-1)	1
Н	yl)amide				
	7-hydroxy-2-phenyl-1H-	2-(2-aminoeth	2	8.71 (1H, d), 8.44 (1H, t), 8.13-7.99 (4H. m), 7.85	358
	benzoimidazole-4-carboxylic	yl)-pyridine			
	acid (2-pyridine-2-yl-ethyl)			3.97 (2H, t), 3.42 (2H, t)	
-	-amide				
71   2   2	2-(4-chloro-phenyl)-7-hydro	phenethylamin 2	2	8 8.03 (2H, d), 7.79 (1H. d), 7.64 (2H m) 7 37–7 15 3	301
	xy-1H-benzoimidazole-4-carb	ø			7
0	oxylic acid phenethyl amide		<del></del>		
c					
? ? ?	Z-(4-chioro-phenyl)-7-hydro	4-nitropheneth   2	2 8	6 8.18 (2H, d), 8.05 (2H, d), 7.80 (1H, d), 7.64 (2H, 4;	436
×	xy-1H-benzoimidazole-4-carb	ylamine	<del>-</del>		
0	oxylic acid (4-nitro-phenethyl)		<del></del>		
<u> </u>	-amide				
73 2 2	2-(4-chloro-phenyl)-7-	4-aminophenet 2	<del></del> -	8 8.11 (2H, d), 7.83 (1H, d), 7.64 (2H, d). 7.50 (2H, 40	406
	hydroxy-1H-benzoimidazole-4	hylamine	ਰ		}
<u> </u>	-carboxylic acid (4-amino-		Ŧ		
pr	phenethyl)-amide				

74	2	2-(4-chloro-phenyl)-7-hydro	4-hydroxyphen	2	87.82 (1H d) 773 (2H d) 765 (2H d) 713 (2H d)	404
		xy-1H-benzoimidazole-4-carb			7.00 (1H, d), 6.86 (1H, d), 6.74 (1H, d), 3.71 (2H, t)	) 
	_	oxylic acid (4-hydroxy-			2.87 (2H, t)	
		phenethyl)-amide				
75	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin	2	8 8.08 (2H, d), 7.79 (1H, d), 7.69 (2H, d). 7.29–7.16	484
		xy-1H-benzoimidazole-4-carb	o-ethyl-phenyl		(4H, dd), 6.89 (1H, d), 3.71 (2H, t), 2.95 (2H, t), 2.88	
		oxylic acid [2-(4-methane	)-methanesulfo		(3H, s)	
_		sulfonylamino-phenyl)-ethyl]-	namide	<del>-</del>		
	·	amide		····		
92	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin	2	6 8.08 (2H, d), 7.77 (1H, d), 7.69 (2H, d), 7.55 (1H.	560
		xy-1H-benzoimidazole-4-carb	o-ethyl)-phen			
		oxylic acid {2-[4-(toluene-4	yl]-4-methyl-		t), 2.86 (2H, t), 2.31 (3H, s)	
		-sulfonylamino)-phenyl]-ethyl	benzenesulfona			
		}-amine	mide			
77	2	2-(4-chloro-phenyl)-7-hydro	3-hydroxy	2	8 8.10-7.37 (3H, m), 7.36-6.43 (6H, m), 3.72 (3H,	437
		xy-1H-benzoimidazole-4-carb	-4-methoxy-p			
		oxylic acid (3-hydroxy-4-	henethylamine			
		methoxy-phenethyl)-amide				
	7			$\dashv$		

400	536	498	452
6 8.16 (2H, d), 7.88 (1H, d), 7.70 (2H, d), 6.94 (1H, d), 4.14-3.92 (2H, m), 3.90 (2H, t), 3.89-3.72 (2H, m), 3.84-3.57 (2H, m), 3.48 (2H, t), 3.30-3.04 (2H, m)	6 8.10 (2H, d), 7.91-7.85 (4H, m), 7.80 (1H, d), 7.68 (2H, m), 6.98 (1H, d), 7.40 (4H, dd), 6.93 (1H, m), 3.75 (2H, t), 3.07 (2H, t)	6 8.13-8.05 (3H, m), 7.80-7.65 (3H, m), 7.28-7.16 (4H, m), 3.69 (2H, t), 2.99 (2H, q), 2.89 (2H, t), 1.28 (3H, t)	6 8.83 (1H, d), 8.11-8.05 (1H, m), 7.86-7.81 (3H, m), 7.68-7.60 (2H, m), 6.90 (1H, d), 6.60-6.54 (1H, d), 3.71-3.60 (4H, m)
2	72	8	2
4-(2-aminoeth yl)morpholine	2-[4-(2-amino -ethyl)-phenyl l-isoindole-1, 3-dione	N-[4-(2-amin o-ethyl)-phen yl]-ethanesulf onamide	2-(2-aminoeth ylamino)-5-nit ropyridine
2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid (2-morpholin-4-yl -ethyl)-amide	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid -2-[4-(1,3-dioxo- 1,3-dihydro-isoindole-2-yl)-p henyl]-ethyl-amide	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid [2-(4-ethane sulfonylamino-phenyl)-ethyl]- amide	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid (5-nitropyridine -2-amino-ethyl)-amide
8	7	α .	2
78	62	80	81

82	2	2-(4-chloro-phenyl)-7-hydro	2-(2-aminoeth 2	8 8.70 (1H, d), 8.43 (1H, t), 8.13-8.09 (3H, m), 8.01	)1 392
		xy-1H-benzoimidazole-4-carb	yl)-pyridine	(1H, d), 7.94 (1H, d), 7.77 (1H, d), 7.61 (2H, d), 4.01	
		oxylic acid (2-pyridine-2-yl-		(2H, t), 3.42 (2H, t)	
		ethyl)-amide			
83	2	2-(4-chloro-phenyl)-7-hydro	histamine 2	6 8.81(s, 1H), 8.12(d, 2H), 7.80(d, 1H), 7.65(d, 2H),	) (c)
		xy-1H-benzoimidazole-4-carb		7.40(s, 1H), 6.83(d, 1H), 3.84(t, 2H), 3.12(t, 2H)	<u>-</u>
		oxylic acid [2-(1H-imidazol-4			<del>.,_</del> _
		-yl)-ethyl]amide			
84	2	2-(4-chloro-phenyl)-7-hydro	4-hydroxyphen 2	8 8.05(d, 2H), 7.79(d, 1H), 7.65(d, 2H), 7.12(d, 2H),	
· <del></del>	-	xy-1H-benzoimidazole-4-carb	ethylamine	6.85(d, 1H), 6.72(d, 2H), 3.70(t, 2H), 2.87(t, 2H)	
		oxylic acid [2-(4-hydroxy			<del></del>
		-phenyl)-ethyl]-amide			
85	2	2-(4-Chloro-phenyl)-7-hydro	4-acetyl-2-py 2	6 8.57(s, 1H), 8.20~8.00(m, 3H), 8.02(br, 1H),	
		xy-1H-benzoimidazole-4-carb	ridylethylamine	7.75~7.60(m, 3H), 7.38(d, 1H), 6.88(d, 1H), 4.12(t,	
		oxylic acid [2-(5-acetylamino		ZH), 3.68(t, ZH), 2.12(s, 3H)	
		-pyridin-2-ylamino)-ethyl]-a			
		mide			

98	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin 2	8 8.03(m, 2H) 7 80(d 1H) 7 60(d 2H) 7 57(d 2H)	
		oxylic acid $(2-\{4-[2-(4- y_1]-2-(4-meth y_1]-3-(4-meth y_1]-3-(4-meth y_1]-3-(4-meth y_1]$	yl]-2-(4-meth	3.10~2.75(m, 13H)	
		methyl-piperazin-1-yl)-acetyl	yl-piperazin-1		
		amino]-phenyl}-ethyl)-amide	-yl)-acetamide		·
87	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin 2	8 8.03(m, 2H), 7.79(d, 1H), 7.61(d, 2H), 7.53(d, 2H)	
		xy-1H-benzoimidazole-4-carb	o-ethyl)-phen	7.29(d, 2H), 6.84(d, 1H), 3.75(t, 2H), 3.34(s, 2H)	
		oxylic acid $(2-\{4-[2-(4-)] 1]-2-(4-ethyl)$	yl]-2-(4-ethyl	3.25(q, 2H), 3.05~2.75(m. 8H), 1.35(t. 3H)	
		ethyl-piperazin-1-yl)-acetyla	-piperazin-1-y		
		mino]-phenyl}-ethyl)-amide	I)-acetamide		
88	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin 2	5 8.03(d, 2H), 7.80(d, 1H), 7.60(d. 2H), 7.54(t. 2H)	
		xy-1H-benzoimidazole-4-carb o-ethyl)-phen	o-ethyl)-phen	7.32(d, 2H), 6.81(d, 1H), 4.08(s, 2H), 3.76(t, 2H)	
		oxylic acid {2-[4-(2-	{2-[4-(2- yl]-2-dimethyl	2.95(m, 8H)	
		dimethylamino-acetylamino)-p	amino-acetami		
		henyl]-ethyl}-amide	đe		

• •	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin	2	\$ 8.02(d, 2H), 7.80(d, 1H), 7.60(d, 2H), 7.54(d, 2H)
		xy-1H-benzoimidazole-4-carb	o-ethyl)-phen		7.32(d, 2H), 6.81(d, 1H), 4.06(s, 2H), 3.77(t, 2H).
		oxylic acid {2-[4-(2-	{2-[4-(2-   yl]-2-diethyla		3.32(q, 4H), 2.99(t, 2H), 1.35(t, 6H)
		diethylamino-acetylamino)-phe	mino-acetamid		
		nyl]-ethyl}-amide	Φ		
8		2-(4-chloro-phenyl)-7-hydro	4-aminophenet	2	6 8.13(d, 2H), 7.78(d, 1H), 7.62(d, 2H), 7.51(d. 2H).
	-	xy-1H-benzoimidazole-4-carb	hylamine	<del></del>	7.29(d, 2H), 6.77(d, 1H), 3.79(t, 2H), 3.69(t, 2H
		oxylic acid [2-(4-amino			
		-phenyl)-ethyl]-amide			
2		2-(4-chloro-phenyl)-7-hydro	N-(2-amino-et	2	8 8.73(s, 1H), 8.22(d, 1H), 8.09(d, 1H), 7.88(m, 2H),
		xy-1H-benzoimidazole-4-carb	hyl)-pyridine-		7.60(d, 1H), 7.47(d, 1H), 7.13(d, 1H), 6.78(m, 1H),
		oxylic acid [2-(5-amino	2,5-diamine		3.87(t, 2H), 3.75(t, 2H)
		-pyridin-2-ylamino)-ethyl]-a			
		mide			
2		2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin 2	2	5 8.03(d, 2H), 7.80(d, 1H), 7.60(d, 2H), 7.54(d, 2H).
		xy-1H-benzoimidazole-4-carb	o-ethyl)-phen		7.31(d, 2H), 6.81(d, 1H), 3.12(s, 2H), 3.98(br, 4H),
		oxylic acid {2-[4-(2-morpholin   yl]-2-morpholi	yl]-2-morpholi		3.77(t, 2H), 3.44(br, 4H), 2.98(t, 2H)
		-4-yl-acetylamino)-phenyl]-e	n-4-yl-acetam	···········	
		thyl}-amide	ide		

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7	ı.
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5 8.13(d, 2H), 7.78(d, 1H), 7.62(d, 2H), 7.51(d, 2H), 7.29(d, 1H), 6.77(d, 1H), 3.81(t, 2H), 3.15(s, 6H), 3.08(t, 2H)	6 8.06(d, 2H), 7.79(d, 1H), 7.73(d, 2H), 7.28(d, 2H), 6.94(d, 2H), 6.83(d, 1H), 4.31(m, 2H), 3.99(br, 2H), 3.95~3.65(m, 4H), 3.65~3.50(m, 4H), 3.32(m, 2H), 2.95(m, 2H)	δ 8.17(d, 2H), 7.78(d, 1H), 7.40(t, 2H), 7.23(d, 2H), 6.90(m, 3H), 4.25(t, 2H), 3.67(t, 2H), 3.50~3.30(m, 10H), 2.90(m, 5H)	δ 8.05(d, 2H), 7.79(d, 1H), 7.62(d, 2H), 7.18(d, 1H), 07.05(d, 1H), 6.90~6.70(m, 3H), 3.70(t, 2H), 3.02(t, 2H)
2 6 8.13(d, 2H), 7.7 7.29(d, 1H), 6.77 3.08(t, 2H)	2 6 8.06(d, 2H), 7.7 6.94(d, 2H), 6.83 3.95~3.65(m, 4H) 2.95(m, 2H)	2 8 8.17(d, 2H), 7.7 6.90(m, 3H), 4.25 10H), 2.90(m, 5H)	2 6 8.05(d, 2H), 7.7' 07.05(d, 1H), 6.90 2H)
<i>N,N</i> -(dimethyl amino)pheneth ylamine	2-[4-(2-morp holin-4-yl-eth oxy)-phenyl]- ethylamine	2-{4-[2-(4-m) ethyl-piperazin -1-yl)-ethoxy ]-phenyl}-eth ylamine	2-hydroxyphen ethylamine
2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid [2-(4-dimethyl amino-phenyl)-ethyl]-amide	2-(4-chloro-phenyl)-7-hydro 2-[4-(2-morp xy-1H-benzoimidazole-4-carb holin-4-yl-eth oxylic acid {2-[4-(2-morpholin oxy)-phenyl]-4-yl-ethoxy)phenyl]-ethyl}- ethylamine amide	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid (2-{4-[2-(4- methyl-piperazin-1-yl)ethoxy] -phenyl}-ethyl)-amide	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid [2-(2-hydroxy -phenyl)-ethyl]-amide
2	8	N	8
93	94	95	96

	2	2-(4-chloro-phenyl)-7-hydro	2-methoxyphe	2	8 8.00(d, 2H), 7.81(d, 1H), 7.57(d, 2H), 7.24(d, 1H),	
		xy-1H-benzoimidazole-4-carb	nethylamine		6.95(m, 1H), 6.85(m, 1H), 6.73(d, 2H), 3.76(s, 3H),	
		oxylic acid [2-(2-methoxy			3.64(t, 2H), 2.98(t, 2H)	
- 1		-phenyl)-ethyl]-amide				
	2	2-(4-chloro-phenyl)-7-hydro	3-bromophene	2	8 8.00(d, 2H), 7.79(d, 1H), 7.02~7.50(m, 3H),	
		xy-1H-benzoimidazole-4-carb	thylamine		7.40~7.20(m, 3H), 6.74(d, 1H), 3.81(t, 2H), 3.01(t,	
		oxylic acid [2-(3-bromo-			2H)	
		phenyl)-ethyl]-amide				-
	3	2-(2,4-dichloro-phenyl)-7-hy	phenethylamin	2	6 7.92-7.66 (3H, m), 7.65-7.38 (1H, m), 7.37-7.00	425
		droxy-1H-benzoimidazole-4-c	ø		(5H, m), 7.44-7.18 (5H, m), 6.85 (1H, d), 3.68 (2H, t),	
		arboxylic acid phenethyl-amide		• • • • • • • • • • • • • • • • • • • •	2.98 (2H, t)	
100	3	2-(2,4-dichloro-phenyl)-7-	4-nitropheneth	2	6 8.08 (2H, d), 7.90-7.31 (5H, m), 7.20-6.97 (1H,	470
		hydroxy-1H-benzoimidazole-4	ylamine		m), 6.82 (1H, d), 3.76 (2H, t), 3.09 (2H, t)	<del></del>
		-carboxylic acid(4-amino-				
		phenethyl)-amide				
101	က	2-(2,4-dichloro-phenyl)-7-	4-hydroxy-3-	2	6 7.95-7.68 (3H, m), 7.67-7.40 (2H, m), 7.20-6.92	471
		hydroxy-1H-benzoimidazole-4	methoxyphenet		(1H, m), 6.82 (2H, t), 6.68 (1H, d), 3.72 (2H, t), 3.60	
_		-carboxylic acid (4-hydroxy	hylamine		(3H, s), 2.88 (2H, t)	
		-3-methoxy-phenethyl)-amide				
7						

	2 (2,4 dicillol 0 phenyl) = 1 =	3-hydroxy-4-	2	8 8.10-7.37 (3H m) 7.36-6 43 (6H m) 3.79 (3H	171
	hydroxy-1H-benzoimidazole-4	methoxyphenet		s), 3.70 (2H, t), 2.81 (2H, t)	<del>-</del>
	-carboxylic acid (3-hydroxy	hylamine			
	-4-methoxy-phenethyl)-amide				
	2-(2,4-dichloro-phenyl)-7-	ethylenediamin	2	8 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 7.37-7.23	364
	hydroxy-1H-benzoimidazole-4	ψ	·	(4H, m), 6.92 (1H, d), 3.77 (2H, t), 3.25 (2H, t)	
	-carboxylic acid (2-amino-				
	ethyl)–amide				
	2-(2,4-dichloro-phenyl)-7-	4-hydroxyphen	<u> </u>		441
	hydroxy-1H-benzoimidazole-4	ethylamine			
	-carboxylic acid (4-hydroxy			2.82 (2H, t)	
	phenethyl)-amide				
<del> </del>	2-(2,4-dichloro-phenyl)-7-	N-[4-(2-amin 2	+		594
	hydroxy-1H-benzoimidazole-4	o-ethyl)-phem	<u> </u>		! )
	-carboxylic acid {2-[4-	phenyl]-4-met		(2H, m), 3.81-3.52 (2H, m), 3.10-2.73 (2H, m), 3.01	
	(toluene-4-sulfonylamino)-phe	hyl-benzensulf		(1H, t), 2.88 (1H, t), 2.48 (3H, s)	
	nyl]-ethyl}-amide	onamide			
	m m		hydroxy-1H-benzoimidazole-4 methoxyphenet  -carboxylic acid (3-hydroxy hylamine  -4-methoxy-phenethyl)-amide  2-(2,4-dichloro-phenyl)-7- ethylenediamin hydroxy-1H-benzoimidazole-4 e  -carboxylic acid (2-amino- ethyl)-amide  2-(2,4-dichloro-phenyl)-7- 4-hydroxyphen hydroxy-1H-benzoimidazole-4 ethylamine  -carboxylic acid (4-hydroxy phenethyl)-amide  2-(2,4-dichloro-phenyl)-7- N-[4-(2-amin hydroxy-1H-benzoimidazole-4 o-ethyl)-phem  -carboxylic acid {2-[4- phenyl]-4-met (toluene-4-sulfonylamino)-phe hyl-benzensulf nyl]-ethyl}-amide	hydroxy-1H-benzoimidazole-4 methoxyphenet  -carboxylic acid (3-hydroxy hylamine  -4-methoxy-phenethyl)-amide  2-(2,4-dichloro-phenyl)-7- ethylenediamin 2  hydroxy-1H-benzoimidazole-4 e  -carboxylic acid (2-amino- ethyl)-amide  2-(2,4-dichloro-phenyl)-7- 4-hydroxyphen 2  hydroxy-1H-benzoimidazole-4 ethylamine  -carboxylic acid (4-hydroxy phenethyl)-amide  2-(2,4-dichloro-phenyl)-7- N-[4-(2-amin 2) hydroxy-1H-benzoimidazole-4 o-ethyl)-phem  -carboxylic acid {2-[4- phenyl]-4-met (toluene-4-sulfonylamino)-phe hyl-benzensulf nył]-ethyl}-amide	hydroxy-1H-benzoimidazole-4 methoxyphenet  -carboxylic acid (3-hydroxy hylamine  -4-methoxy-phenethyl)-amide  2-(2,4-dichloro-phenyl)-7- ethylenediamin 2  hydroxy-1H-benzoimidazole-4 ethylamine  -carboxylic acid (2-amino-  ethyl)-amide  2-(2,4-dichloro-phenyl)-7- 4-hydroxyphen 2  hydroxy-1H-benzoimidazole-4 ethylamine  -carboxylic acid (4-hydroxy  phenethyl)-amide  2-(2,4-dichloro-phenyl)-7- N-[4-(2-amin 2 6  hydroxy-1H-benzoimidazole-4 o-ethyl)-phem  -carboxylic acid {2-[4- phenyl]-4-met (toluene-4-sulfonylamino)-phe hyl-benzensulf (toluene-4-sulfonylamino)-phe hyl-benzensulf onamide

901	က	2-(2,4-dichloro-phenyl)-7-	<i>N</i> -[4-(2-amin	2	6 7.92-7.78 (3H, m), 7.68 (1H, d), 7.24 (4H, dd),	518
		hydroxy-1H-benzoimidazole-4	o-ethyl)-phen		6.96 (1H, d), 3.68 (2H, t), 2.93 (2H, t), 2.90 (3H, s)	
		-carboxylic acid	acid yl]-methanesul			
		[2-(4-methanesulfonylamino-p	fonamide			
		henyl)-ethyl]-amide				
107	က	2-(2,4-dichloro-phenyl)-7-	2-[4-(2-amino	2	6 7.92-7.83 (7H, m), 7.67 (1H, d), 7.38 (4H, dd),	570
		hydroxy-1H-benzoimidazole-4	-ethyl)-phenyl		6.98 (1H, d), 3.72 (2H, t), 3.05 (2H, t)	
		-carboxylic acid {2-[4-(1,3	]-isoindole-1,			
		-dioxo-1,3-dihydro-isoindol-2	3-dione			
		-yl)-phenyl]-ethyl}-amide				
				+		
108	က	2-(2,4-dichloro-phenyl)-7-	4-(2-aminoeth	2	6 8.02-7.80 (3H, m), 7.65 (1H, d), 6.98 (1H, d),	434
		hydroxy-1H-benzoimidazole-4	yl) morpholine	·	4.14-3.92 (2H, m), 3.88 (2H, t), 3.89-3.72 (2H, m),	
		-carboxylic acid (2- morpholin			3.84-3.57 (2H, m), 3.44 (2H, t), 3.30-3.04 (2H, m)	
!		-4-yl-ethyl)-amide				
109	3	2-(2,4-dichloro-phenyl)-7-	N-[4-(2-amin 2	2	6 7.91-7.75 (3H, m), 7.68 (1H, d), 7.21 (4H, dd),	532
		hydroxy-1H-benzoimidazole-4	o-ethyl)-phen	<del>-</del>	6.99 (1H, d), 3.66 (2H, t), 2.99 (2H, q), 2.89 (2H, t),	
		-carboxylic acid [2-(4-	yl]-ethanesulf		1.28 (3H, t)	
		ethanesulfonylamino-phenyl)-e	onamide			
		thyl]~amide				

110	က	2-(2,4-dichloro-phenyl)-7-hy 2-(2-aminoeth droxy-1H-benzoimidazole-4-c ylamino)-5-nit arboxylic acid (5- nitropyridine ropyridine -2-amino-ethyl)-amide	2-(2-aminoeth ylamino)-5-nit ropyridine	2	6 8.83 (1H, d), 8.11-8.05 (1H, m), 7.86-7.81 (3H, m), 7.68-7.60 (1H, m), 6.90 (1H, d), 6.60-6.54 (1H, d), 3.71-3.60 (4H, m)	486
111	က	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid (2-pyridin -2-yl-ethyl)-amide	2-(2-aminoeth yl)-pyridine	83	5 8.70 (1H, d), 8.40 (1H, t), 8.07-7.50 (6H, m), 6.83 (1H, d), 3.95 (2H, t), 3.38 (2H, t)	426
112	က	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [2-(4-acetyl amino-phenyl)-ethyl]-amide	4-(acetylamino )phenethylamin e	2 7 8	6 7.85~7.78(m, 3H), 7.61(d, 1H), 7.25(d, 2H), 7.15(d, 2H), 6.86(d, 1H), 3.69(t, 2H), 2.95(t, 2H), 2.88(s, 3H)	
113	င	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [2-(4-pentanoyl amino-phenyl)ethyl]-amide	4-(pentanoyla 2 mino)phenethyl amine		6 7.90~7.80(m, 3H), 7.72(d, 1H), 7.61(d, 2H), 7.20(d, 2H), 6.89(d, 1H), 3.68(t, 2H), 2.89(t, 2H), 2.35(t, 2H), 1.65(m, 2H), 1.38(m, 2H), 0.96(t, 3H)	



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114	4	2-(4-fluoro-phenyl)-7-hydrox	<i>N</i> -[4-(2-amin	2	8 8.15-8.10 (2H, m), 7.78 (1H, d), 7.46 (2H, t), 7.27
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen		(2H, d), 7.18 (2H, d), 6.87 (1H, d), 3.70 (2H, t), 2.97
		xylic acid [2-(4-methane	yl]-methanesul		(2H, t), 2.87 (3H, s)
		sulfonylamino-phenyl)-ethyl]-	fonamide	<del></del> .	
		amide			
115	4	2-(4-fluoro-phenyl)-7-hydrox	N-[4-(2-amin 2	2	
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen		
		xylic acid {2-[4-(toluene-4-	yl]-p-toluenes		
		sulfonylamino)-phenyl]-ethyl}	ulfonamide		
		-amide			
116	4	2-(4-fluoro-phenyl)-7-hydrox	N-[4-(2-amin   2	2	6 8.17 (2H, m), 7.77 (1H, d), 7.44 (2H, t), 7.25 (2H,
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen		d), 7.17 (2H, d), 6.92 (1H, d), 3.67 (2H, t), 3.02 (2H,
		xylic acid [2-(4-ethanesulfonyl yl]-ethanesulf	yl]-ethanesulf		q), 2.96 (2H, t), 1.26 (3H, t)
		amino-phenyl)-ethyl]-amide	onamide		
117	4	2-(4-fluoro-phenyl)-7-hydrox N-[4-(2-amin		2 8	δ 8.1~8.2 (m, 2H), 7.58 (d,1H), 7.44 (m, 4H),
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen		7.34 (m, 2H), 6.92 (d, 1H), 3.66 (t, 2H), 2.90 (t,
		xylic acid [2-(4-acetylamino	yl]-acetamide		2H), 2.09 (s, 1H)
		-phenyl)-ethyl]-amide			



<u>~</u>	2-(4-fluoro-phenyl)-7-hydrox	N-(5-nitro-pyr	2	\$ 8.84(s, 1H), 8.21~8.17(m, 3H) 7.79(d, 1H) 7.44(t)
y-1	y-1H-benzoimidazole-4-carbo	idin-2-yl)-eth		2H), 6.92(d, 1H), 6.63(br, 1H), 3.90~3.60(m, 4H)
X	xylic acid [2-(5-nitro-pyridin	ane-1,2-diami		
-	-2-ylamino)-ethyl]-amide	ne		
7	2-(4-fluoro-phenyl)-7-hydrox	N-[6-(2-Amin	2	8 8.24~8.19(m, 2H), 7.95~7.75(m, 3H), 7.43(t, 2H)
>	y-1H-benzoimidazole-4-carbo	o-ethylamino)-		7.15(d, 1H), 6.92(d, 1H), 3.80~3.65(m. 4H), 2.99(t
×	xylic acid [2-(5-methane	pyridin-3-yl]-		3H)
	sulfonylamino-pyridin-2-ylami	methanesulfon		
2 -	no)-ethyl]-amide	amide		
-	(4.5)			
1	$2 \times 10000 \text{ pileliyi}^{-1} = 119000 \text{ pileliyi}^{-1} = 119000 \text{ pileliyi}^{-1} = 119000 \text{ pileliyi}^{-1} = 119000 \text{ pileliyi}^{-1} = 1190000 \text{ pileliyi}^{-1} = 1190000 \text{ pileliyi}^{-1} = 1190000000000000000000000000000000000$		.7	6 8.23(m, 2H), 7.81(d, 1H), 7.52(m, 4H),
<u>,</u>	y-1H-benzoimidazole-4-carbo	o-ethylamino)-		7.40~7.20(m, 4H), 7.01(d, 1H), 6.82(d, 1H), 3.75(t.
<u> </u>	xylic acid {2-[5-(toluene-	pyridin-3-yl]-		2H), 3.66(t, 2H), 2.36(s, 3H)
4-	4-sulfonylamino)-pyridin-2-yl	p-toluenesulfo		
ап	amino]-ethyl}-amide	namide		
2-	2-(4-fluoro-phenyl)-7-hydrox	histamine	2	6 8.81(s, 1H), 8.19(m, 2H), 7.80(d, 1H)
<u>&gt;</u>	y-1H-benzoimidazole-4-carbo			3.80(£ 2H) 3
-X	xylic acid [2-(1H-imidazol-			2H)
4-	4-yl)-ethyl]-amide			
$\dashv$			_	

2-(4-fluoro-	2-(4-fluoro-	2-(4-fluoro-phenyl)-7-hydrox	N-[6-(2-amin	2	8 8.58(s, 1H), 8.22(m, 2H), 8.04(br, 1H), 7.69(d. 1H)
y-1H-benzoimidazole-4-carbo	y-1H-benzoimidazole-4-	-carbo	o-ethylamino)-		7.50~7.35(m, 3H), 6.90(d, 1H), 4.11(t, 2H), 3.69(t.
xylic acid [2-(5-acetylamino	xylic acid [2-(5-acetylami	ou	pyridin-3-yl]-		2H), 2.11(s, 3H)
-pyridin-2-yl-amino)-ethyl]-a	-pyridin-2-yl-amino)-ethyl	]-a	acetamide		
mide	mide				
2-(4-fluoro-phenyl)-7-hydrox	2-(4-fluoro-phenyl)-7-hydrox	ير	N-[4-(2-amin 2	2	8 8.10~7.80(m, 2H), 7.69(d, 1H), 7.43(d. 2H), 7.25(t.
y-1H-benzoimidazole-4-carbo	y-1H-benzoimidazole-4-carbo		o-ethyl)-phen		2H), 7.19(d, 2H), 6.76(d, 1H), 3.63(t, 2H), 3.21(s,
xylic acid (2-{4-[2-(4-	xylic acid (2-{4-[2-(4-		yl]-2-(4-meth		2H), 2.90~2.78(m, 13H)
methyl-piperazin-1-yl)-acetyl	methyl-piperazin-1-yl)-acetyl		yl-piperazin-1		
amino]-phenyl}-ethyl)-amide	amino]-phenyl}-ethyl)-amide		-yl)-acetamide		
		•	N-[4-(2-amin 2	2	8 8.13(m, 2H), 7.79(d, 1H), 7.52(d, 2H), 7.37(t, 2H),
рo		٠.	o-ethyl)-phen		7.27(d, 2H), 6.85(d, 1H), 3.72(t, 2H), 3.30(s, 2H),
xylic acid (2-{4-[2-(4-ethyl			yl]-2-(4-ethyl		3.24(q, 2H), 3.05~2.85(m, 10H), 1.35(t, 3H)
-piperazin-1-yl)-acetylamino]			-piperazin-1-y		
-phenyl}-ethyl)-amide		_	1)-acetamide		
2-(4-fluoro-phenyl)-7-hydrox	2-(4-fluoro-phenyl)-7-hydrox		N-[4-(2-amin 2		6 8.11(m, 2H), 7.78(d, 1H), 7.53(d, 2H).
y-1H-benzoimidazole-4-carbo		_	o-ethyl)-phen		:
xylic acid {2-[4-(2-dimethyl			yl]-2-dimethyl		2H), 2.94(m, 8H)
amino-acetylamino)-phenyl]-	amino-acetylamino)-phenyl]-		amino~acetami		
ethyl}-amide	ethyl}-amide	_	de		

8 8.13(m, 2H), 7.79(d, 1H), 7.54(d, 2H), 7.39(t, 2H), 7.30(d, 2H), 6.86(d, 1H), 4.08(s, 2H), 3.72(t, 2H), 3.33(q, 4H), 2.96(t, 2H), 1.35(t, 6H)	5 8.20(m, 2H), 7.79(d, 1H), 7.49(d, 2H), 7.42(t, 2H), 7.32(d, 2H), 6.86(d, 1H), 3.74(t, 2H), 3.06(t, 2H)	5 8.14(m, 2H), 7.78(d, 1H), 7.41(d, 2H), 7.35(d, 1H), 7.14(d, 2H), 6.85(d, 1H), 3.89(m, 4H), 3.71(t, 2H), 3.28(m, 4H), 2.96(t, 2H)	6 8.13 (m, 1H), 7.78 (d, 1H), 7.32~7.20 (m, 4H), 7.11 (s, 1H), 6.74 (m, 2H), 6.48 (d, 1H), 3.60 (t, 2H), 2.90 (t, 2H), 2.82~2.71 (m, 6H), 2.40 (q, 4H), 1.65 (m, 1H), 1.02 (t, 6H)
8	2	2	2
N-[4-(2-amin o-ethyl)-phen yl]-2-diethyla mino-acetamid e	4-aminophenet hylamine	2-(4-morpholi n-4-yl-phenyl) -ethylamine	{1-[4-(2-amin o-ethyl)-phen yl]-pyrrolidin-3-yl}-diethyl-amine
2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(2-diethyl amino-acetylamino)-phenyl]-e thyl}-amide	2-(4-fluoro-phenyl)-7-hydrox 4-aminopy-1H-benzoimidazole-4-carbo hylamine xylic acid [2-(4-amino-phenyl)-ethyl]-amide	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-morpholin -4-yl-phenyl)-ethyl]-amide	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(3-diethyl amino-pyrrolidin-1-yl)-phenyl ]-ethyl}-amide
4	4	4 .	4
130	131	132	133

2-(4-fily-1H-type) xylic acymorpho	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(2- morpholin-4-yl-acetylamino)-	N-[4-(2-amin o-ethyl)-phen yl]-2-morpholi n-4-yl-acetam	8	6 8.15(m, 2H), 7.79(d, 1H), 7.53(d, 2H), 7.39(t, 2H), 7.29(d, 2H), 6.87(d, 1H), 4.13(s, 2H), 3.97(br, 4H), 3.72(q, 2H), 3.44(br, 4H), 2.97(t, 2H)
phenyl]-ethyl}-amide	-amide			
y-1H-benzoimidazole-4-xylic acid [2-(4-dimethylamino-phenyl)-ethyl]-am	y-1H-benzoimidazole-4-carbo amino)phenethyl xylic acid [2-(4-dimethyl amino-phenyl)-ethyl]-amide	N,N-(dimethyl amino)pheneth ylamine	8	8 8.20(m, 3H), 7.78(d, 1H), 7.54(m, 3H), 7.43(t, 2H), 6.84(d, 1H), 3.75(t, 2H), 3.21(s, 6H), 3.07(t, 2H)
2-(4-fluoro-ph y-1H-benzoimi xylic acid (2-[4-4-yl-ethoxy)amide	2-(4-fluoro-phenyl)-7-hydrox 2-[4-(2-morp y-1H-benzoimidazole-4-carbo holin-4-yl-eth xylic acid {2-[4-(2-morpholin oxy)-phenyl]4-yl-ethoxy)-phenyl]-ethyl} ethylamine -amide		2	5 8.18(m, 2H), 7.79(d, 1H), 7.42(t, 2H), 7.26(d, 2H), 7.00~6.85(m, 3H), 4.33(m, 2H), 4.10~4.00(br, 2H), 3.95~3.75(br, 2H), 3.75~3.50(m, 8H), 3.32(m, 4H), 2.95(m, 2H)
2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(2-hydroxy -phenyl)-ethyl]-amide	nyl)-7-hydrox azole-4-carbo hydroxy amide	2-hydroxyphen 2 ethylamine	2 7 8	6 8.18(m, 2H), 7.78(d, 1H), 7.38(t, 2H), 7.14(d, 1H), 7.03(d, 1H), 6.88~6.74(m, 3H), 3.77(t, 2H), 2.98(t, 2H)

138	4	2-(4-fluoro-phenyl)-7-hydrox	2-methoxyphe 2	8 8.18~8.05(m. 2H). 7.78(d. 1H). 7.45~7.25(m. 3H)
		y-1H-benzoimidazole-4-carbo	nethylamine	7.20(m, 2H), 6.95(d, 1H), 6.82(d, 1H), 3.78(s, 3H)
		xylic acid [2-(2-methoxy-		3.73(t, 2H), 2.99(t, 2H)
		phenyl)-ethyl]-amide		
139	4	2-(4-fluoro-phenyl)-7-hydrox	3-bromophene 2	8 8.12(m, 2H), 7.80(d, 1H), 7.49(s, 1H)
		y-1H-benzoimidazole-4-carbo	thylamine	, 5H), 6.83(d, 1H), 3.76(t, 2H), 2
		xylic acid [2-(3-bromo-		2H)
		phenyl)-ethyl]-amide		
140	5	2-(2,4-difluoro-phenyl)-7-hyd N-[4-(2-amin	N-[4-(2-amin 2	6 7.92-7.89 (1Н, m), 7.74 (1Н, m), 7.30-7.11 (6Н
		roxy-1H-benzoimidazole-4-ca	o-ethyl)-phen	m), 6.74 (1H, d), 3.67 (2H, bs), 2.89 (2H, bs) 2.82
		rboxylic acid [2-(4-methane	yl]-methanesul	(3H, s)
		sulfonylamino-phenyl)-ethyl]-	fonamide	
		amide		
141	2	2-(2,4-difluoro-phenyl)-7-hyd	N-[4-(2-amin 2	6 7.99 (1H, m), 7.74 (1H, d), 7.50 (2H, d), 7.33-7.26
		roxy-1H-benzoimidazole-4-ca	o-ethyl)-phen	(2H, m), 7.23 (4H, m), 6.94 (2H. d). 6.81 (1H. d) 3.58
		rboxylic acid {2-[4-(toluene	yl]-p-toluenes	(2H, t), 2.82 (2H, t), 2.23 (3H, s)
		-4-sulfonylamino)-phenyl]-et	ulfonamide	
		hyl}amide		

z-(z,4-uiiiuoro-pnenyi)-/-hyd
roxy-1H-benzoimidazole-4-ca
rboxylic acid [2-(4-ethane
sulfonylamino-phenyl)-ethyl]-
amide
2-(2-chloro-4-fluoro-phenyl)
-7-hydroxy-1H-benzoimidazol
e-4-carboxylic acid yl]-methanesul
[2-(4-methanesulfonylamino-p
henyl)-ethyl]-amide
2-(2-chloro-4-fluoro-phenyl)
-7-hydroxy-1H-benzoimidazol
e-4-carboxylic acid
{2-[4-(toluene-4-sulfonylami
no)-phenyl]-ethyl}amide
2-(2-chloro-4-fluoro-phenyl)
-7-hydroxy-1H-benzoimidazol
e-4-carboxylic acid
[2-(4-ethanesulfonylamino-ph
enyl)-ethyl]-amide

	6   2-(2-chloro-4-fluoro-phenyl)		2-(2-chloro-4-fluoro-ph	-(2-chloro-4-fluoro-ph	(lyna	N-[1-(9-0)	C	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
2 2 2	(If it is a second of the seco	(If it is a second of the seco	_	_	±1 ^7	(2 animii	v	o 8.00~7.31(m, ZH), 7.57(d, 1H), 7.48~7.34(m, 3H),
2 2 2	-'/-hydroxy-1H-benzoimidazol   o-eth				o-eth	o-ethyl)-phen		7.19(d, 2H), 6.92(d, 1H), 3.66(t, 2H), 2.9(t, 2H),
8 8 8	e-4-carboxylic acid [2-(4- yl]-a				yl]-a	yl]-acetamide		2.09(s, 3H)
η η η η η η η η η η η η η η η η η η η	acetylamino-phenyl)-ethyl]-a	acetylamino-phenyl)-ethyl]-a	acetylamino-phenyl)-ethyl]-a	etylamino-phenyl)-ethyl]-a				
8 8 8	mide	mide	mide	de				
8 2 2	6   2-(2-chloro-4-fluoro-phenyl)   2-n				2-n	2-morpholin-4	<del> </del>	8 8.00~7.90(m, 2H), 7.60(d, 1H), 7.43(t, 1H), 6.95(d.
8 2 3	-7-hydroxy-1H-benzoimidazol -yl				-yl	-yl-ethylamine		1H), 4.20~3.60(m, 8H), 3.46(t, 2H), 3.34~3.10(br.
8 8	e-4-carboxylic acid (2-	e-4-carboxylic acid (2-	e-4-carboxylic acid (2-	4-carboxylic acid (2-				2H)
8 8	morpholin-4-yl-ethyl)-amide	morpholin-4-yl-ethyl)-amide	morpholin-4-yl-ethyl)-amide	rpholin-4-yl-ethyl)-amide				
8	6 2-(2-chloro-4-fluoro-phenyl) 2-(				2-(	2-(4-methyl-p	<del>                                     </del>	8 7.98(m, 2H), 7.59(d, 1H), 7.40(t. 1H), 6.93(d 1H)
8	-7-hydroxy-1H-benzoimidazol jper				iper	iperazin-1-yl)		3.80~3.50(br, 10H), 3.21(t, 2H), 2.95(s, 3H), 2.06(t.
0	e-4-carboxylic acid -eth	acid	acid	acid	-eth	-ethylamine		ZH)
0	[2-(4-methyl-piperazin-1-yl)	[2-(4-methyl-piperazin-1-yl)	[2-(4-methyl-piperazin-1-yl)	-(4-methyl-piperazin-1-yl)				
8	-ethyl]-amide	-ethyl]-amide	-ethyl]-amide	thyl]-amide				
	6 2-(2-chloro-4-fluoro-phenyl) pent	<del>                                     </del>	<del>                                     </del>	<del>                                     </del>	pent		<del></del>	5 7.92~7.82(m, 2H), 7.57(d, 1H), 7.46~7.37(m, 3H).
	-7-hydroxy-1H-benzoimidazol   [4-(2-amino-e	-7-hydroxy-1H-benzoimidazol   [4-(	-7-hydroxy-1H-benzoimidazol [4-	-hydroxy-1H-benzoimidazol	[4-(	(2-amino-e		7.20(d, 2H), 6.92(d, 1H), 3.66(t, 2H), 2.91(t, 2H).
	e-4-carboxylic acid thyl)	acid	acid	acid	thyl)	thyl)-phenyl]-		2.34(t, 2H), 1.66(m, 2H), 1.40(m, 2H), 0.95(t, 3H)
	[2-(4-pentanoylamino-phenyl) amide				amid	 		
	-ethyl]-amide	-ethyl]-amide	-ethyl]-amide	hyl]-amide				

8 7.92~7.83(m, 2H), 7.62(d, 1H), 7.43(t, 1H), 7.07(d, 2H), 6.94(d, 1H), 6.69(d, 2H), 3.62(t, 2H), 2.85(t, 2H)	6 8.85(s, 1H), 8.12(br, 1H), 7.79~7.85(m, 3H), 7.63(d, 1H), 7.42(t, 1H), 6.95(d, 1H), 6.62(br, 1H), 3.90~3.60(m, 4H)	8 8.05~7.85(m, 3H), 7.79(d, 1H), 7.61(d, 1H), 7.42(t, 1H), 7.14(d, 1H), 6.94(d, 1H), 3.80~3.60(m, 4H), 2.92(t, 3H)	6 7.92(m, 1H), 7.89(d, 1H), 7.58(d, 2H), 7.45(m, 3H), 7.29(m, 3H), 6.92(d, 1H), 6.78(d, 1H), 3.72(t, 2H), 3.61(t, 2H), 2.37(s, 3H)
2	5	2	N
4-hydroxyphen ethylamine	N-(5-nitro-pyr idin-2-yl)-eth ane-1,2-diami ne	N-[6-(2-amin o-ethylamino)-pyridin-3-yl]-methanesulfon amide	N-[6-(2-amin o-ethylamino)-pyridin-3-yl]-p-toluenesulfo
2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [2-(4- hydroxy-phenyl)-ethyl]-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [2-(5-nitro-pyridin-2-ylamino)-ethyl]-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [2-(5-methanesulfonylamino-pyridin -2-ylamino)-ethyl]-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid {2-[5- (toluene-4-sulfonylamino)-pyr idin-2-ylamino]-ethyl}-amide
ဖ	9	9	9
150	151	152	153

154	9	2-(2-chloro-4-fluoro-phenyl)	histamine 2	8 8.79(s, 1H), 8.00~7.0 2H), 7.62(d 1H)
		-7-hydroxy-1H-benzoimidazol		7.50~7.35(m, 2H), 6.93(d, 1H), 3.76(t, 2H), 3.76(t.
	-	e-4-carboxylic acid [2-(1H-		2H), 3.10(t, 2H)
		imidazol-4-yl)-ethyl]-amide		
155	9	2-(2-chloro-4-fluoro-phenyl) N-[6-(2-amin	N-[6-(2-amin 2	8 8.57(s, 1H), 8.10~7.95(m, 2H), 7.88(d, 1H),
		-7-hydroxy-1H-benzoimidazol o-ethylamino)-	o-ethylamino)-	7.74(d, 1H), 7.50~7.30(m, 2H), 6.95(d, 1H), 4.10(t,
		e-4-carboxylic acid	acid pyridin-3-yl]-	2H), 3.65(t, 2H), 2.13(s, 3H)
		[2-(5-acetylamino-pyridin-2-	acetamide	
		ylamino)-ethyl]-amide		
156	9	2-(2-chloro-4-fluoro-phenyl)	<i>N</i> -[4-(2-Amin 2	8 7.97~7.80(m, 2H), 7.61(d, 1H), 7.59(d, 2H), 7.40(t.
		-7-hydroxy-1H-benzoimidazol o-ethyl)-phen	o-ethyl)-phen	1H), 7.25(d, 2H), 6.92(d, 1H), 3.67(t, 2H), 3.34(s,
		e-4-carboxylic acid (2-{4-[2	yl]-2-(4-meth	2H), 3.10~2.75(m, 13H)
		-(4-methyl-piperazin-1-yl)-a	yl-piperazin-1	
		cetylamino]-phenyl}-ethyl)-a	-yl)-acetamide	
		mide		

	9	2-(2-chloro-4-fluoro-phenyl)	N-[4-(2-amin	2	8 7.97~7.83(m, 2H), 7.61(d, 1H), 7.50(d, 2H), 7.39(t)
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen		1H), 7.25(d, 2H), 6.91(d, 1H), 3.67(t, 2H), 3.34(s.
		e-4-carboxylic acid (2-{4-[2-	yl]-2-(4-ethyl		4H), 3.21(q, 2H), 3.05~2.75(m, 8H), 1.35(t, 3H)
		(4-ethyl-piperazin-1-yl)-acet	-piperazin-1-y		
		ylamino]-phenyl}-ethyl)-amid	1)-acetamide		
- 1		O.			
	9	2-(2-chloro-4-fluoro-phenyl)	N-[4-(2-amin	2	8 7.99(m, 1H), 7.84~7.70(m, 2H), 7.52(d, 2H)
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen		7.35~7.25(m, 3H), 6.77(d, 1H), 4.08(s, 2H), 3.73(s,
		e-4-carboxylic acid {2-[4-(2	yl]-2-dimethyl		2H), 2.97(m, 8H)
		-dimethylamino-acetylamino)-	amino-acetami		
		phenyl]-ethyl}-amide	qe		
	9	2-(2-chloro-4-fluoro-phenyl)	<i>N</i> -[4-(2-amin 2	2	8 7.94~7.82(m, 2H), 7.60(d, 1H), 7.52(d, 2H), 7.40(t
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen		1H), 7.28(d, 2H), 6.89(d, 1H), 4.08(s, 2H), 3.68(t.
		e-4-carboxylic acid	yl]-2-diethyla		2H), 3.31(q, 4H), 2.94(t, 2H), 1.34(t, 6H)
		{2-[4-(2-diethylamino-acetyla mino-acetamid	mino-acetamid		
		mino)-phenyl]-ethyl}-amide	Φ		
	7	2-(3-chloro-4-fluoro-phenyl)	N-[4-(2-amin 2	2	(1H, d), 7.90 (1H, m), 7.72 (1H, d), 7.47 (2H. d), 7.39
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen		(1H, m), 7.13–7.06 (4H, m), 6.95(2H, d), 6.75 (1H. d)
		e-4-carboxylic acid	yl]-p-toluenes		3.63 (2H, t), 2.85 (2H, t), 2.23 (3H, s)
		{2-[4-(toluene-4-sulfonylami	ulfonamide		
		no)-phenyl]-ethyl}amide			

					309			310			378				361			
6 8.19 (1H, d), 7.95 (1H, m), 7.74 (1H, d), 7.42 (1H.	t), 7.24 (2H, d), 7.13 (2H, d), 6.75 (1H, d), 3.68 (2H,	t), 2.91 (2H, t), 2.81 (3H, s)			6 7.95-7.70 (2H, m), 7.69 (1H, d), 7.60-7.42 (1H,	m), 7.41-7.23 (2H, m), 3.42 (2H, t), 1.78-1.56 (2H,	m), 1.55–1.34 (2H, t), 0.97 (3H, t)	8 8.10 (1H, d), 7.90 (1H, d), 7.68 (1H, d), 7.67-7.53	(3H, m), 6.81 (1H, d), 3.65 (2H, t), 3.22-3.00 (2H, t),	2.05 (2H, t)	8 8.04 (1H, d), 7.81 (1H, d), 7.75-7.66 (3H, m), 6.96	(1H, d), 6.87 (1H, d), 3.53-3.41 (6H, m), 2.39 (2H, t),	2.03 (2H, t), 1.90 (2H, m)		6 9.05 (1H, s), 8.17 (2H, d), 7.84 (1H, d), 7.75 (1H,	s), 7.72-7.62 (3H, m), 7.55 (1H, s), 6.88 (1H, d), 4.40	(2H, t), 3.57 (2H, t), 2.28 (2H, m)	
2					က			3	က		3				3			
<i>N</i> -[4-(2-amin	o-ethyl)-phen	yl]-methanesul	fonamide		n-butylamine			1,3-diaminopro	pane		1-(3-aminopro	pyl)-2-prolidin	one		1-(3-aminopro	pyl)imidazole		
2-(3-chloro-4-fluoro-phenyl)	-7-hydroxy-1H-benzoimidazol	e-4-carboxylic acid	[2-(4-methanesulfonylamino-p	henyl)-ethyl]-amide	7-hydroxy-2-phenyl-1H-benz	oimidazole-4-carboxylic acid	butylamide	7-Hydroxy-2-phenyl-1H-ben	zoimidazole-4-carboxylic acid	(3-amino-propyl)-amide	7-hydroxy-2-phenyl-1H-benz	oimidazole-4-carboxylic acid	[3-(2-oxo-prolidine-1-yl)-pr	opyl]-amide	7-hydroxy -2- phenyl-1H-	benzoimidazole-4-carboxylic	acid (3-imidazol-1-yl-propyl)	-amide
2								Н			1				1			- <u>-</u> -
161					162			163		Ī	164				165			<u>.</u>

380		343	412	395
6 8.20-8.11 (2H, m), 7.86 (2H, d), 7.84-7.69 (1H, m), 7.63-7.59 (2H, m), 4.10 (2H, t), 4.06 (2H, t), 3.80 (2H, t), 3.65 (2H, t), 3.54 (2H, t), 3.15 (2H, t), 2.14	(2H, m) 8 8.18-8.11 (2H, m), 7.84 (1H, d), 7.73-7.63 (4H, m), 7.40 (1H, d), 6.89 (1H, d), 4.28 (2H, t), 3.59 (2H, t), 2.63 (3H, s), 2.25 (2H, m)	5 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 6.92 (1H, d), 3.42 (2H, t), 1.78-1.56 (2H, m), 1.55-1.34 (2H, t), 0.97 (3H, t)	6 8.21-8.11 (2H, m), 7.82 (1H, d), 7.63-7.53 (2H, m), 6.86 (1H, m), 3.60-3.38 (6H, m), 2.38 (2H, t), 2.03 (2H, t), 1.89 (2H, m)	6 9.03 (1H, d), 8.18 (2H, t), 7.81 (1H, d), 7.74 (1H, d), 7.64-7.53 (3H, m), 6.84 (1H, d), 4.40 (2H, t), 3.60 (2H, t), 2.29 (2H, m)
က	က	m	က	m
4-(3-aminopro pyl)morphorine	3-(2-methyl-i midazol-1-yl)- propylamine	n-butylamine	1-(3-aminopro pyl)-2-pyrrolid one	1-(3-aminopro pyl)imidazole
7-hydroxy-2- phenyl-1H-benzoimidazole-4-carboxylicacid (3-morphorine-4-yl-	propyl)-amide 7-hydroxy-2-phenyl-1H-benz oimidazole-4-carboxylic acid [3-(2-methyl-imidazol-1-yl)- propyl]-amide	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid butylamide	2-(4-chloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid [3-(2-oxo- prolidin-1-yl)-propyl]-amide	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid (3-imidazole-1-yl
	H	2	23	0
166	167	168	169	170

rb pyl)-morphorin  yl e  3-(2-phenyl-i 3 4  rb midazol-1-yl)-  propylamine  propylamine  -propylamine  3-(4,5-dichlor 3 8  0-imidazoel-1 6  -yl)-propylami  ne  3-(2-methyl-i 3 8  3-(2-methyl-i 3 8  3-(2-methyl-i 3 8	171	2	2-(4-chloro-phenyl)-7-hydro	4-(3-aminonro	8 8 91 – 8 10 (9U m) 7 0E (111 3) 7 0E (211 4)	
oxylic acid (3-morphorine-4-yl e  -propyl)-amide  2			xy-1H-benzoimidazole-4-carb	pyl)-morphorin	m), 6.80 (1H, d), 4.05 (2H, t), 3.81 (2H, t), 3.68–3.46	414
2 2-(4-chloro-phenyl)-7-hydro 3-(2-phenyl-i 3 xy-1H-benzoimidazole-4-carb midazol-1-yl)-oxylic acid [3-(2-pentyl- propylamine imidazol-1-yl)-propyl]-amide	···		oxylic acid (3-morphorine-4-yl		(4H, m), 3.17 (2H, t), 2.11 (2H, m)	
xy-1H-benzoimidazole-4-carb midazol-1-yl)- oxylic acid [3-(2-pentyl- imidazol-1-yl)-propyl]-amide  z-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(4-methyl- imidazol-1-yl)-propyl]-amide  z-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb o-imidazoel-1 oxylic acid [3-(4,5-dichloro- yl)-propylamie imidazol-1-yl)-propyl]-amide  z-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb o-imidazol-1-yl) imidazol-1-yl)-propyl]-amide  z-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(2-methyl- oxylic acid [3-(3-(3-methyl- oxylic acid [3-(3-(3-(3-(3-(3-(3-(3-(3-(3-(3-(3-(3-(3			-propyl)-amide	_		
xy-1H-benzoimidazole-4-carb midazol-1-yl)- oxylic acid [3-(2-pentyl- imidazol-1-yl)-propyl]-amide  2	172	-2	2-(4-chloro-phenyl)-7-hydro	<del>                                     </del>	8 8.13 (2H, d), 7.87 (1H, d), 7.70 (1H, d). 7.64-7.53	473
oxylic acid [3–(2–pentyl– propylamine imidazol–1–yl)–propyl]–amide  2			xy-1H-benzoimidazole-4-carb	midazol-1-yl)-		
imidazol-1-yl)-propyl]-amide  2			oxylic acid [3-(2-pentyl-	propylamine	3.53 (1H, t), 2.27 (2H, m)	
2 2-(4-chloro-phenyl)-7-hydro 3-(4-methyl-i 3 xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(4-methyl- amide imidazol-1-yl)-propyl]-amide imidazol-1-yl)-propyl]-amide 2-(4-chloro-phenyl)-7-hydro 3-(4,5-dichlor 3 xy-1H-benzoimidazole-4-carb o-imidazol-1 oxylic acid [3-(4,5-dichloroyl)-propyl]-amide ne imidazol-1-yl)-propyl]-amide ne xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(2-methyl- amide imidazol-1-yl)-propyl]	•		imidazol-1-yl)-propyl]-amide			
xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(4-methyl- imidazol-1-yl)-propyl]-amide  2	173	2	2-(4-chloro-phenyl)-7-hydro	_	8 8.85 (1H, d), 8.17 (2H, t). 7.87 (1H, m) 7 68–7 57 4	409
oxylic acid [3-(4-methyl- imidazol-1-yl)-propyl]-amide  2			xy-1H-benzoimidazole-4-carb	midazole-1-yl)		2
imidazol-1-yl)-propyl]-amide  2			oxylic acid [3-(4-methyl-	-propylamine	(2H, m), 2.37–2.20 (5H, m)	
2 2-(4-chloro-phenyl)-7-hydro 3-(4,5-dichlor 3 xy-1H-benzoimidazole-4-carb o-imidazoel-1 oxylic acid [3-(4,5-dichloroyl)-propylami imidazol-1-yl)-propyl]-amide ne  2 2-(4-chloro-phenyl)-7-hydro 3-(2-methyl-i 3 xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(2-methylpropylamine imidazol-1-yl)-propyl			imidazol-1-yl)-propyl]-amide			•
xy-1H-benzoimidazole-4-carb o-imidazoel-1 oxylic acid [3-(4,5-dichloroyl)-propylami imidazol-1-yl)-propyl]-amide ne  2 2-(4-chloro-phenyl)-7-hydro 3-(2-methyl-i 3 xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(2-methyl- imidazol-1-yl)-propyl	174	2	2-(4-chloro-phenyl)-7-hydro	+	8 8.13 (2H, t), 7.85–7.78 (2H, m), 7.65–7.55 (2H m) 4.	474
oxylic acid [3-(4,5-dichloroyl)-propylami imidazol-1-yl)-propyl]-amide ne  2 2-(4-chloro-phenyl)-7-hydro 3-(2-methyl-i 3 xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(2-methylpropylamine imidazol-1-yl)-propyl			xy-1H-benzoimidazole-4-carb	o-imidazoel-1		+
imidazol-1-yl)-propyl]-amide ne  2			oxylic acid [3-(4,5-dichloro-	-yl)-propylami		
2 2-(4-chloro-phenyl)-7-hydro 3-(2-methyl-i 3 xy-1H-benzoimidazole-4-carb midazole-1-yl) oxylic acid [3-(2-methylpropylamine imidazol-1-yl)-propylamine			imidazol-1-yl)-propyl]-amide	ne		
midazole-1-yl) -propylamine	175	2	2-(4-chloro-phenyl)-7-hydro	+-	6 8.21-8.09 (3H, m), 7.68 (1H. d). 7.60-7.55 (3H	421
-propylamine			xy-1H-benzoimidazole-4-carb	midazole-1-yl)		
			oxylic acid [3-(2-methyl-	-propylamine	s), 2.28 (2H, m)	
animae di piopiti animae			imidazol-1-yl)-propyl]-amide			<del></del>

176	က	2-(2,4-dichloro-phenyl)-7-	n-butylamine	3	6 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 7.37-7.23	377
<del></del>		hydroxy-1H-benzoimidazole-4				-
		-carboxylic acid butylamide			1.55-1.34 (2H, t), 0.97 (3H, t)	
177	က	2-(2,4-dichloro-phenyl)-7-	1-(3-aminopro	3	8 8.07-7.74 (3H, m), 7.73-7.49 (1H m) 6 90 (1H	778
		hydroxy-1H-benzoimidazole-4	pyl)-2-pyrolidi			) †
		-carboxylic acid [3-(2-0xo-	one		(2H, m)	
		pyrolidin-1-yl)-propyl]-amide				
178	က	2-(2,4-dichloro-phenyl)-7-	1-(3-aminopro	8	6 9.02 (1H, s), 7.90-7.72 (4H m) 7 64-7 46 (9H	190
		hydroxy-1H-benzoimidazole-4 pyl)imidazole	pyl)imidazole			23
		-carboxylic acid (3-imidazol			m)	
		-1-yl-propyl)-amide				
179	က	2-(2,4-dichloro-phenyl)-7-	4-(3-aminopro 3	$\dagger$	8 8.03-7.76 (3H. m), 7.75-7.45 (1H m), 6.85 (1Ll d	740
		hydroxy-1H-benzoimidazole-4	pyl)morphorine			 p
		-carboxylic acid (3-morphorin-	· · · · · · · · · · · · · · · · · · ·		(2H, t), 2.11 (2H, m)	-
		4-yl-propyl)-amide				
180	က	2-(2,4-dichloro-phenyl)-7-hy	3-(2-phenyl-i 3	_	8 15 (d 2H) 8 11 6 111 2/367 (H) 8 15 (d 2H)	
		droxy-1H-benzoimidazole-4-c	midazol-1-yl)-		7.20.7.25 (m. 211), 65 (13 111), 7.30 (8, 111), 7.34~7.29 (m, 2H),	
		arboxylic acid [3-(2-phenyl-	propylamine		7.27 - 1.23 (III, 311), 0.30 (G, 1H), 4.41 (f, 2H), 3.53 (f, 2H),	
		imidazol-1-yl)-propyl]-amide		7	2.27 (q, 3H)	

	T		
6 8.84 (s, 1H), 7.91~7.73 (m, 3H), 7.58 (m, 1H), 7.38 (s, 1H), 6.85 (d, 1H), 4.29 (t, 2H), 3.54 (t, 2H), 2.34~2.25 (m, 5H)	6 7.91~7.81 (m, 4H), 7.52 (s, 1H), 6.96 (d, 1H), 4.15 (t, 2H), 3.64 (t, 2H), 2.13 (q, 2H)	6 8.11~8.09 (m, 3H), 7.61 (m, 2H), 7.45 (s, 1H), 6.88 (d, 1H), 4.31 (t, 2H), 3.46 (t, 2H), 2.25 (q, 2H), 2.33 (s, 3H)	6 8.10~8.05 (m, 3H), 7.58 (m, 2H), 7.40 (s, 1H), 6.88 (d, 1H), 4.22 (t, 2H), 3.60 (t, 2H), 3.02 (m, 1H), 1.3 (s, 6H)
က	е .	က	က
3-(4-methyl-i midazol-1-yl)- propylamine	3-(4,5-dichlor o-imidazol-1- yl)-propylamin e	3-(2-methyl-i midazol-1-yl)- propylamine	3-(2-isopropyl -imidazol-1-yl )-propylamine
2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [3-(4-methyl-imidazol-1-yl)-propyl]-amide	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-carboxylic acid [3-(4,5-dichloro-imidazol-1-yl)-propyl l-amide	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-carboxylic acid [3-(2-methylimidazol-1-yl)-propyl]-amide	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylicacid [3-(2- isopropyl-imidazol-1-yl)-prop yl]-amide
ო	င	က	င
181	182	183	184

4-fluoro-phenyl)-7-	2-(4-fluoro-phenyl)-7-hydrox
H-benzoimidazole-4-carbo pyl)imidazole	y-1H-benzoimidazole-4-carbo pyl)im
c acid (3-imidazol-1-yl-	xylic acid (3-imidazol-1-yl-
yyl)–amide	propyl)-amide
t-fluoro-phenyl)-7-hydrox 3-(2-isopropyl	2-(4-fluoro-phenyl)-7-hydrox   3-(2
H-benzoimidazole-4-carbo   -imidazol-1-yl	y-1H-benzoimidazole-4-carbo   -imi
s acid [3-(2-isopropyl- )-propylamine	xylic acid [3-(2-isopropyl- )-p
azol-1-yl)-propyl]-amide	imidazol-1-yl)-propyl]-amide
-fluoro-phenyl)-7-hydrox 3-(4-methyl-	2-(4-fluoro-phenyl)-7-hydrox 3-(4
1-benzoimidazole-4-carbo   imidazol-1-yl)	y-1H-benzoimidazole-4-carbo imid
acid [3-(4-methyl-	xylic acid [3-(4-methyl-
azol-1-yl)-propyl]-amide	imidazol-1-yl)-propyl]-amide
-fluoro-phenyl)-7-hydrox 3-(2-methyl-	2-(4-fluoro-phenyl)-7-hydrox   3-(2
$1$ -benzoimidazole- $4$ -carbo $\mid$ imidazol- $1$ -yl)	y $-1$ H $-$ benzoimidazole $-$ 4 $-$ carbo $\mid$ imid
acid [3-(2-methyl-	xylic acid [3-(2-methyl-
tzol-1-yl)-propyl]-amide	imidazol-1-yl)-propyl]-amide
-fluoro-phenyl)-7-hydrox 3-(2-ethyl-	2-(4-fluoro-phenyl)-7-hydrox 3-(2
I-benzoimidazole-4-carbo   imidazol-1-yl)	y–1H–benzoimidazole–4–carbo $ig $ imid
acid [3-(2-ethyl-	xylic acid $[3-(2-\text{ethyl}-$
	imidazol-1-yl)-propyl]-amide

	<del></del>		<del></del>
6 8.24-8.16 (2H, m), 8.04 (1H, d), 7.79 (1H, d), 7.45-7.33 (2H, m), 6.99-6.84 (1H, m), 4.18 (2H, t), 3.54 (2H, t), 2.18 (2H, m)	5 8.20 (1H, q), 8.18-7.97 (1H, m), 7.86 (1H, d), 7.64 (1H, s). 7.45 (1H, s), 7.39-7.24 (1H, m), 6.86 (1H, d), 4.33(2H, t), 3.60 (2H, t), 3.49 (1H, m), 2.26 (2H, t), 1.36 (3H, s), 1.34 (3H, s)	5 8.23 (1H, q), 7.13-7.97 (1H, m), 7.84 (1H, d), 7.74 (1H, s), 7.56 (1H, s), 7.31-7.24 (2H, m), 6.84 (1H, d), 4.40(2H, t), 3.56 (2H, t), 2.28 (2H, t)	5 8.22 (1H, q), 8.14-7.98 (1H, m), 7.84 (1H, d), 7.40-7.27 (3H, m), 6.85 (1H, d), 4.30 (2H, t), 3.57 (2H, t), 2.30 (5H, m)
က	(n)	က	က
3-(4,5-dichlor o-imidazol-1-yl)-propylamin	3-(2-isopropyl -imidazol-1-yl )-propylamine	1-(3-aminopro pyl)imidazole	3-(4-methyl-imidazol-1-yl) -propylamine
2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [3-(4,5-dichloro- imidazol-1-yl)-propyl]-amide	2-(2,4-difluoro-phenyl)-7-hyd roxy-1H-benzoimidazole-4-carboxylic acid [3-(2-isopropyl-imidazol-1-yl)-propyl]-amide	2-(2,4-difluoro-phenyl)-7-hyd roxy-1H-benzoimidazole-4-ca rboxylic acid (3-imidazol -1-yl-propyl)-amide	2-(2,4-difluoro-phenyl)-7-hyd roxy-1H-benzoimidazole-4-ca rboxylic acid [3-(4-methyl- imidazol-1-yl)-propyl]-amide
4	വ	വ	വ
190	191	192	193

5 2-(2,4-difluoro-phenyl)-7-hyd	2-(2,4-difluoro-pher	nyl)-7-hyd	3-(4,5-dichlor	က	6 8.19-8.03 (2H, m), 7.81 (2H, m), 7.39-7.29 (1H,
roxy-1H-benzoimidazole-4-ca		0-ii	o-imidazol-1-		m), 6.85 (1H, d), 4.17 (2H, t), 3.52 (2H, t), 2.16 (2H,
rboxylic acid [3-(4,5-dichloro-   yl)-	rboxylic acid [3-(4,5-dichloro-   yl)-	y1)-	yl)-propylamin		t)
imidazol-1-yl)-propyl]-amide e	$\dashv$	e)			
5 $2-(2,4-\text{difluoro-phenyl})-7-\text{hyd}$ 3-			3-(2-methyl-	3	6 8.21 (1H, q), 8.06 (1H, m), 7.85(1H, d), 7.62
roxy-1H-benzoimidazole-4-ca imi		<u>.</u> []	imidazol-1-yl)		(1H,s). 7.39-7.27 (2H, m), 6.87 (1H, d), 4.30(2H, t),
rboxylic acid [3-(2-methylpi		ď	-propylamine		3.58 (2H, t), 2.63 (3H, s), 2.25 (2H, t)
imidazol-1-yl)-propyl]-amide	imidazol-1-yl)-propyl]-amide			····	
5 $2-(2,4-\text{difluoro-phenyl})-7-\text{hyd}$ 3-(	2-(2,4-difluoro-phenyl)-7-hyd 3-(	3–(	3-(2-ethyl-	m	8 8.29-8.05 (2H, m), 7.86 (1H, d), 7.64 (1H,s). 7.43
roxy-1H-benzoimidazole-4-ca imic		imi	imidazol-1-yl)	<del>_</del> _	(1H, s), 7.38-7.31 (1H, m), 6.95 (1H, d), 4.29 (2H, t),
rboxylic acid [3-(2-ethyl-	<u>.                                    </u>	_pr	-propylamine		3.57 (2H, t), 3.03 (2H, q), 2.25 (2H, t), 1.34 (3H, t)
imidazol-1-yl)-propyl]-amide	imidazol-1-yl)-propyl]-amide	•			
5 $2-(2,4-\text{difluoro-phenyl})-7-\text{hyd}$ 3-(		3–(	3-(4,5-dichlor 3	3 8	6 8.19-8.03 (2H, m), 7.81 (2H, m), 7.39-7.29 (1H,
roxy-1H-benzoimidazole-4-ca o-i		0-1	o-imidazol-1	<del></del>	m), 6.85 (1H, d), 4.17 (2H, t), 3.52 (2H, t), 2.16 (2H,
rboxylic   acid   -yl)	acid	-y1)	-yl)-propylami	<del></del>	t)
[3-(4,5-dichloro-imidazol-1-y ne		ne		<del></del>	
1)-propyl]-amide	l)-propyl]-amide				

			T
6 9.05 (1H, s), 8.00-7.88 (2H, m), 7.74 (1H, s), 7.66-7.57 (2H, m), 7.46-7.41 (1H, m), 6.95 (1H, d), 4.38(2H, t), 3.52 (2H, t), 2.25 (2H, t)	5 8.88 (1H, s), 8.00-7.87 (2H, m), 7.60 (1H, m), 7.41 (2H, m). 6.94 (1H, d), 4.28 (2H, t), 3.54 (2H, t), 2.29 (3H, s), 2.22 (2H, t)	5 7.94 (1H, m), 7.85 (1H, m), 7.76 (1H, s), 7.48 (1H, d). 7.30 (1H, t), 6.76 (1H, d), 4.17 (2H, t), 3.56 (2H, t), 2.16 (2H, t)	6 7.83 (1H, m), 7.50(1H, m), 7.39 (1H, s), 7.23 (2H, m), 7.13(1H, s), 6.76 (1H, d), 4.20(2H, t), 3.57 (2H, t), 2.47 (3H, s), 2.03 (2H, t)
က	m	m	m
1–(3–aminopro pyl) imidazole	3-(4-methyl-imidazol-1-yl) -propylamine	3-(4,5-dichlor o-imidazol -1-yl)-propyla mine	3-(2-methyl-imidazol-1-yl) -propylamine
2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid (3- imidazol-1-yl-propyl)-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [3-(4-methyl-imidazol-1-yl)- propyl]-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [3-(4,5 -dichloro-imidazol-1-yl)-prop yl]-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [3-(2-methyl-imidazol-1-yl)- propyl]-amide
9	9	9	9
198	199	200	201

202	2	2-(3-chloro-4-fluoro-phenyl)   3-(4-methyl-	3-(4-methyl- 3	8 8.87 (1H, s), 8.37	8 8.87 (1H, s), 8.37 (1H, d), 8.17 (1H, m), 7.83 (1H,	
		-7-hydroxy-1H-benzoimidazol	imidazol	d), 7.59 (1H, t), 7.4	d), 7.59 (1H, t), 7.40(1H, s), 6.84 (1H, d), 4.33 (2H,	
		e-4-carboxylic acid	acid  -1-yl)-propyla	t), 3.60 (2H, t), 2.25 (5H, m)	5 (5H, m)	<del>-</del>
		[3-(4-methyl-imidazol-1-yl)-	mine			
		propyl]-amide				
203	2	2-(3-chloro-4-fluoro-phenyl)   1-(3-aminopro   3   6 9.05 (1H, s), 8.37 (1H, d), 8.17 (1H, m), 7.83 (1H,	1-(3-aminopro	8 9.05 (1H, s), 8.37	7 (1H, d), 8.17 (1H, m), 7.83 (1H,	
		-7-hydroxy-1H-benzoimidazol pyl) imidazole	pyl) imidazole	m), 7.75 (1H, s), 7	m), 7.75 (1H, s), 7.61-7.43 (2H, m), 6.82 (1H, d),	
		e-4-carboxylic acid (3-		4.41 (2H, t), 3.60 (2H, t), 2.30 (2H, t)	2H, t), 2.30 (2H, t)	
		imidazol-1-yl-propyl)-amide				

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Example 204: Preparation 7-hydroxy-2-[4-(2-morpholin-4-ylof ethylamino)-phenyl]-1H-benzoimidazole-4-carboxylic acid [3-(4,5-dichloroimidazol-1-yl)-propyl]-amide

(1) Preparation of 3-[(4-nitro-benzimidoyl)-amino]-4-methoxy-benzoic acid 5 methyl ester

Anhydrous p-toluenesulfonic acid (6.30 g, 33.1 mmol) was added to 50 ml of benzene and the resulting mixture was refluxed while removing water using a dean-stock trap. Added thereto were 3-amino-4-methoxy 10 benzoic acid methyl ester (3 g, 16.6 mmol) obtained in step 1 of Preparation Example 1 and 4-nitrobenzonitrile (2.94 g, 19.9 mol), followed by stirring at 160 °C for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding NaHCO3 thereto, extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (2.83 g, 8.59 mmol) in a yield of 52%.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.12-8.09 (m, 2H), 7.82 (d,1H), 7.70-7.69 (m, 20 1H), 6.98 (d, 1H), 4.91 (bs, 2H), 3.89(s, 6H)
  - Preparation of 2-(4-nitro-phenyl)-7-methoxy-1H-benzoimidazole-4carboxylic acid methyl ester

3-[(4-nitro-benzimidoyl)-amino]-4-methoxy-benzoic acid ester (1.63 g, 4.95 mmol) was dissolved in 50% methanol, and 5% NaOCl was added dropwise thereto at room temperature. After checking the reaction by TLC, Na<sub>2</sub>CO<sub>3</sub> (1.05 g, 9.38 mmol) was added dropwise thereto and refluxed for 40 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate and the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (0.75 g, 2.28 mmol) in a yield of 46 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.90 (bs, 1H), 8.36-8.31 (m, 4H), 7.95 (d, 1H), 6.78 (d, 1H), 4.16 (s, 3H), 4.01 (s, 3H)

- (3) Preparation of 2-(4-amino-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid
- 2-(4-nitro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (0.63 g, 1.92 mmol) obtained in step 2 was dissolved in 15 ml of EtOH, 0.1 g of 10% Pd/C was added thereto and stirred for 24 hours while hydrogen was supplied thereto from a balloon fulfilled with H<sub>2</sub> gas. The resulting solution was filtered and dried to obtain the title compound (0.57 g, 1.92 mmol) in a yield of 100%.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-*d*<sub>4</sub>): δ 10.48 (bs, 1H), 7.93 (d, 2H), 7.82 (d, 1H), 6.77 (d, 2H), 6.71 (d, 1H), 4.11 (s,3H), 3.98 (s, 3H)

- (4) Preparation of 2-[(2-morpholinoethyl)-4-amino-phenyl]-7-methoxy-1Hbenzoimidazole-4-carboxylic acid methyl ester
- 2-(4-amino-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (160 mg, 0.54 mmol) obtained in step 3 was dissolved in DMF, cesium carbonate (0.53 g, 1.61 mmol) was added thereto and stirred for 5 min.

  20 Added thereto were 2-chloroethylmorpholine (0.12g, 0.64mmol) and potassium iodide (0.18g, 1.08mmol), followed by stirring for 24 hours. Then, the resulting solution was extracted with ethyl acetate, the extract was concentrated under a reduced pressure, and the residue was purified by silica gel chromatography to obtain the title compound (91 mg, 0.22 mmol) in a yield of 41 %.

 $^{1}$ H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 7.97 (d, 1H), 7.57 (d, 2H), 6.77-6.73 (m, 3H), 4.54 (t, 2H), 4.11 (s, 3H), 3.99 (s, 3H), 3.57-3.55(m, 4H), 2.64 (t, 2H), 2.31-2.28 (m, 4H)

- (5) Preparation of 2-[(2-morpholinoethyl)-4-amino-phenyl]-7-methoxy-1H-benzoimidazole-4-carboxylic acid-[3-(4,5-dichloro-imidazol-1-yl)-propyl]-amide
- 2-[(2-morpholinoethyl)-4-amino-phenyl]-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (22 mg, 0.05 mmol) was dissolved in THF/H<sub>2</sub>O, LiOHH<sub>2</sub>O (6.7mg, 0.16mmol) was added thereto and

stirred at room temperature. The resulting solution was filtered to remove residual LiOHH<sub>2</sub>O, and the solvent was removed. The residue was dried and dissolved in DMF. Added thereto were 4,5-dichloro-1-(3-aminopropyl)imidazole (12.5mg, 0.06mmol), EDCI (30.9mg, 0.16mmol), DMAP (65.6mg, 0.54mmol) and HOBt (21.8mg, 0.16mmol), followed by stirring at room temperature. The resulting solution was extracted with ethyl acetate and concentrated under a reduced pressure. The resulting residue was purified by silica gel chromatography to obtain the title compound (19 mg, 0.03 mmol) in a yield of 63 %.

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 $^{1}$ H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 7.93 (d, 1H), 7.77- 7.75 (m, 3H), 7.52 (d, 2H), 6.92 (d, 1H), 4.17 (t, 2H), 4.06-4.02 (m, 5H), 3.58-3.56 (m, 4H), 3.50 (t, 2H), 2.66 (t, 2H), 2.31-2.29 (m, 4H), 2.16 (q, 2H)

15 (6) Preparation of 2-[(2-morpholinoethyl)-4-amino-phenyl]-7-hydroxy-1H-benzoimidazole-4-carboxylic acid-[3-(4,5-dichloro-imidazol-1-yl)-propyl]-amide

2-[(2-morpholinoethyl)-4-amino-phenyl]-7-methoxy-1H-

benzoimidazole-4-carboxylic acid-[3-(4,5-dichloro-imidazol-1-yl)-propyl]-amide (15 mg, 0.03 mmol) obtained in step 5 was dissolved in MC, BBr<sub>3</sub> (1.0M solution in MC, 0.3mL, 0.3mmol) was added thereto and stirred at room temperature for 48 hours. The reaction was stopped by adding water thereto and the resulting solution was extracted with MC/MeOH (7:1). The extract was concentrated under a reduced pressure and purified by silica gel chromatography to obtain the title compound (5.9 mg, 0.01 mmol) in a yield of 40 %.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 7.95 (d, 1H), 7.81- 7.79 (m, 4H), 7.55 (d, 1H), 6.94 (d, 1H), 4.15 (t, 2H), 3.94 (t, 2H), 3.59 (t, 2H), 3.58-3.56 (m, 4H), 2.64 (t, 2H), 2.32-2.30 (m, 4H), 2.18 (q, 2H)

## Test Example 1: Assay for GSK-3β inhibiting activity

The GSK-3β inhibiting activity was determined in accordance with the method of Shultz et al. described in US Patent No. 6153618, with minor modifications by using phospho-CREB peptide as a substrate.

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First, PCR (polymerase chain reaction) was carried out using human DNA as a template as well as primers which were designed to correspond to the 3'- and 5' ends of the polynucleotide coding human GSK-3ß gene (Genbank Accession No.: L33801). The BamH1/XhoI fragment of the amplified PCR product thus obtained was inserted into the pGex vector between the BamH1 and XhoI sites, and the vector obtained was transformed into E. coli BL21(DE3). The transformed cells thus obtained was incubated in LB agar plates (1% Bacto-trypton, 0.5% yeast extract, 1% NaCl) containing ampicillin (100  $\mu$ l/ml) until the optical density at 600nm reached about 0.5. The cultured mixture was cooled to 18 °C and isopropyl β-Dthiogalacto-pyranoside (IPTG) was added thereto to a final concentration of 0.5 mM. After 16 hours, the resultant was centrifuged at 10,000 x g for 10 min, the collected cells were suspended in a buffer solution (30 mM Tris-HCl (pH 7.5), 100 mM NaCl, 5% glycerol, 2mM DTT) and the cells were disrupted using Sonic Dismembrator (Fisher, U.S.A.) in a ice bath. The resulting solution was centrifuged at 16,000 rpm for 30 minutes. The supernatant was connected to GST (Glutathione-S-transferase) column (Pharmacia Biotech, U.S.A.) equilibrated in the same buffer solution, purified by glutathione affinity chromatography (eluent: 5 mM glutathione), and then, digested with thrombin to cleave the connecting site between the GST moiety and GSK-3β protein. The purified GSK-3β protein was diluted in a buffer solution (20 mM HEPES (pH 7.5), 5% glycerol, 2 mM DTT) to a final concentration of 50 mM NaCl and the resulting solution was subjected to mono S column chromatography (eluent: linear gradient from 0M to 1M NaCl buffer) using mono S column (Pharmacia Biotech, U.S.A.) equilibrated in the same buffer solution to obtain GSK-3\beta protein.

100 nM GSK-3 $\beta$  protein, 12.5 mM each of the compounds prepared in Examples 1 to 204 dissolved in DMSO, an assay buffer (50 mM Tris-HCl, pH 7.5, 10mM MgCl<sub>2</sub>, 1mM EGTA, 1mM DTT), 100  $\mu$ M phospho-CREB peptide (NEB, USA), 100  $\mu$ M ATP, <sup>32</sup>P-ATP and 1  $\mu$  Ci were reacted at 30 °C for 1 hour. The reaction was stopped by adding  $5\mu$ l of 5% phosphoric acid to 25  $\mu$ l of the resulting solution. The resulting mixture was centrifuged at 15,000 rpm for 10 min, 20  $\mu$ l of the supernatant was added dropwise to Whatman p81 filter paper, and then, the resulting filter paper was washed with 0.5% phosphate buffer for 10 min. The filter paper was further washed 3 times and the enzymatic activity was determined by examining the extent of phospho-CREB peptide phosphorylation which is

represented by the unit of count per minute (CPM), measured with a  $\beta$ -counter (Packard, USA).

The GSK-3 $\beta$  inhibiting activity was then calculated in accordance with the following equation:

$$CPM(sample) - CPM(blank)$$
Degree of Inhibition (%) = 100 x [ 1 - ----- ]
$$CPM(control) - CPM(blank)$$

wherein the blank represents a value obtained without the use of the enzyme and the compound of the present invention, and the control, in the absence of the compound of the present invention.

The  $IC_{50}$  value of the inventive compound was determined from the degree of inhibition (%) and the result is shown in Table 3.

Table 3

Exam.	IC <sub>50</sub> (µ M)	Exam.	IC <sub>50</sub> (µ M)	Exam.	IC <sub>50</sub> (µ M)	Exam.	IC <sub>50</sub> (µ M)
1	>1	52	>1	103	>5	154	>1
2	>1	53	>1	104	>1	155	>1
3	>1	54	>1	105	0.05	156	0.28
4	>1	55	>1	106	0.015	157	0.49
5	0.3	56	0.7	107	0.05	158	0.23
6	>1	57	0.58	108	>1	159	0.68
7	>1	58	0.67	109	0.03	160	>1
8	>1	59	0.16	110	0.28	161	0.09
9	0.18	60	0.35	111	>1	162	0.24
10	0.04	61	>1	112	0.04	163	>1
11	>5	62	>1	113	0.19	164	0.84
12	0.2	63	0.45	114	0.001	165	0.08
13	0.36	64	0.03	115	0.026	166	>1

14	>1	65	0.06	116	0.003	167	0.1
15	0.11	66	>1	117	<del> </del>	<del></del>	0.1
16	0.7	67	<del> </del>	<del> </del>	0.03	168	> 1
<b></b>		<del> </del>	0.16	118	>5	169	>1
17	0.24	68	0.017	119	>5	170	0.19
18	>1	69	>1	120	0.07	171	>1
19	>1	70	>1	121	0.03	172	0.8
20	4.1	71	>1	122	0.2	173	0.1
21	>5	72	0.12	123	0.05	174	0.04
22	>1	73	>1	124	0.07	175	0.28
23	0.68	74	>1	125	>1	176	0.45
24	>5	75	0.009	126	>1	177	0.2
25	>1	76	0.05	127	0.18	178	0.04
26	>1	77	0.033	128	0.15	179	>1
27	>1	78	>1	129	0.12	180	0.21
28	0.74	79	0.12	130	0.33	181	0.03
29	0.08	80	0.07	131	0.17	182	0.008
30	>1	81	>1	132	0.19	183	0.06
31	>1	82	>1	133	>1	184	0.15
32	0.5	83	>1	134	0.04	185	>1
33	>1	84	>1	135	>1	186	0.05
34	>1	85	>5	136	0.24	187	0.01
35	0.007	86	0.25	137	0.005	188	0.002
36	>1	87	0.23	138	>1	189	>1
37	>1	88	0.22	139	0.12	190	0.006
38	>1	89	0.32	140	> 1	191	0.09

		Τ					
39	>1	90	0.13	141	0.043	192	0.008
40	>1	91	>1	142	0.001	193	0.02
41	>1	92	0.08	143	0.002	194	0.004
42	>1	93	>1	144	0.006	195	0.03
43	>1	94	>5	145	0.002	196	0.02
44	>1	95	>1	146	0.07	197	0.003
45	0.02	96	0.022	147	0.21	198	0.02
46	>5	97	0.17	148	>1	199	0.01
47	>5	98	>1	149	0.14	200	0.002
48	>5	99	1	150	0.06	201	0.07
49	0.6	100	0.2	151	0.4	202	0.009
50	0.6	101	>1	152	0.24	203	0.003
51	0.87	102	0.23	153	0.05	204	>5

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

What is claimed is

1. A compound of formula (I), and a pharmaceutically acceptable salt, hydrate, solvate or isomer thereof:

wherein:

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n is 0, 1, 2 or 3;

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen, hydroxy, halogen or morpholin-1-yl-ethylamino;

R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen;

linear or cyclic C<sub>1</sub>-C<sub>6</sub> alkyl optionally having one or more substituents, the carbon of the alkyl being optionally replaced with nitrogen, sulfur or oxygen, wherein the substituent is: hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido; alkanesulfonyl; amido; an aromatic group optionally having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino. alkylamino, carboxyl, nitro, amido, dioxoisoindole sulfonylamino; an aromatic group having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido, the aromatic ring having nitrogen, sulfur or oxygen; or cyclic C<sub>3</sub>-C<sub>8</sub> alkyl optionally having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido;

an aromatic group optionally having one or more substituents, the aromatic ring having optional nitrogen, sulfur or oxygen, wherein the substituent is; hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido, alkanesulfonyl; amido; or linear or cyclic C<sub>1</sub>-C<sub>6</sub> alkyl optionally having one or more substituents, the alkyl having an optional nitrogen, sulfur or oxygen linkage and the substituent of the alkyl

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being: hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido, alkanesulfonyl; amido; an aromatic group optionally having one or more substituents selected from the group consisting of hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; amido; dioxoisoindole; and a sulfonylamino having an aromatic group substituted with hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, sulfonylamido, alkanesulfonyl or amido; an aromatic group optionally having one or more substituents selected form the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, sulfonylamide, alkanesulfonyl and amido, the aromatic ring containing nitrogen, sulfur or oxygen; or a cyclic C<sub>3</sub>-C<sub>8</sub> alkyl optionally having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido; or

form, together with the -N-(CH<sub>2</sub>)<sub>n</sub>- moiety to which they are attached, a nitrogen heterocycle optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, the heterocycle containing optional nitrogen or oxygen.

2. The compound of claim 1, wherein  $R^4$  and  $R^5$  are each independently hydrogen;

C<sub>1</sub>-C<sub>4</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH2, NO2, and an aromatic group, the aromatic group optionally having one or more substituents selected from the group consisting of OH, C<sub>1</sub>-C<sub>4</sub> alkyloxy, NH<sub>2</sub>, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino and dioxoisoindole; cyclic C<sub>3</sub>-C<sub>8</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>; C<sub>1</sub>-C<sub>4</sub> alkyl carrying a morpholine or oxopyrolidine group which is optionally substituted with OH, NH2, NO2 or -O-; C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> aminoalkyl carrying a pyrrol, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, isoxazole, oxazole, isotiazole, tiazolidine, tiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, 1,2,5-thiodiazole, thiodiazole, 1,3,4-oxadiazole, 1,3,4-thiodiazole, pyridine, pyrimidine or triazine group which is optionally having one or more substituents selected from the group consisting of Cl, OH, NH2, NO2, C1-C4 and phenyl;

cyclic C<sub>3</sub>-C<sub>8</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>;

an aromatic group optionally having one or more substituents selected



from the group consisting of OH; NH<sub>2</sub>; hydroxyalkyl; aminoalkyl; NO<sub>2</sub>; and a C<sub>1</sub>-C<sub>4</sub> alkyl group optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino, dioxoisoindole and thiophensulfonylamino; or

form, together with the -N- $(CH_2)_n$ - moiety to which they are attached, a nitrogen heterocycle optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>, the heterocycle containing 1 to 3 nitrogen, sulfur or oxygen atom.

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3. The compound of claim 1, wherein  $R^4$  and  $R^5$  are each independently hydrogen;

C<sub>1</sub>-C<sub>4</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, morpholine, nitropyridineamino, pyridine, oxopyrolidin, imidazole optionally having a Cl, CH<sub>3</sub> or phenyl substituent; and phenyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, methoxy, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino and dioxoisoindole;

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cyclic  $C_3$ - $C_8$  alkyl optionally having one or more substituents selected from the group consisting of OH,  $NH_2$  and  $NO_2$ ;

phenyl optionally having one or more substituents selected from the group consisting of OH; NH<sub>2</sub>; NO<sub>2</sub>; and C<sub>1</sub>-C<sub>4</sub> alkyl optionally having a OH, NH<sub>2</sub>, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino, dioxoisoindole or thiophensulfonylamino substituent; or

form, together with -N-(CH<sub>2</sub>)<sub>n</sub>- moiety to which they are attached, a piperidine ring optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>.

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4. A process for preparing the compound of formula (IA) which comprises the steps of:

reacting 3-amino-4-methoxy benzoic acid (compound II) and an alcohol to obtain compound (III);

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adding anhydrous p-toluenesulfonic acid and benzonitrile to the compound (III) thus obtained, refluxing the mixture at 80 to 200  $^{\circ}$ C, adding NaOCl thereto at room temperature and purifying by silica gel column

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chromatography to obtain compound (IV);

dissolving the compound (IV) thus obtained in an alcohol, adding an aqueous alkali solution thereto and refluxing the mixture to obtain compound (V);

dissolving the compound (V) thus obtained in an organic solvent, adding a Lewis acid thereto and refluxing the mixture to obtain compound (VI);

dissolving the compound (V) thus obtained in alcohol, adding a strong acid thereto at room temperature and refluxing the mixture to obtain compound (VII);

dissolving the compound (VII) thus obtained and (4-bromomethylphenoxy)-methyl polystyrene Wang resin in an organic solvent, adding a base and KI thereto and stirring the mixture at 50 to 60 °C for 1 to 24 hours to obtain compound (VIII);

dissolving the compound (VIII) thus obtained in an organic solvent, adding an alcohol solution of an alkali hydroxide thereto and refluxing the mixture to obtain compound (IX);

dissolving the compound (IX) thus obtained in an organic solvent, adding  $R^4N(CH_2)_nR^5$  and a coupling agent thereto and stirring the mixture at room temperature to obtain compound (X); and

dissolving the compound (X) thus obtained in CH<sub>2</sub>Cl<sub>2</sub>, adding trifluoroacetic acid thereto and stirring the mixture at room temperature to obtain compound (Ia).

II

35 OH 
$$R^3$$
  $R^3$   $VI$ 

10 OCH<sub>8</sub>

$$R^3$$

$$R^1$$

$$R^2$$

$$VIII$$

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$$\stackrel{\text{O}}{\underset{\text{N}}{\bigvee}} \stackrel{\text{OH}}{\underset{\text{R}^1}{\bigvee}} \stackrel{\text{R}^3}{\underset{\text{R}^2}{\bigvee}}$$

X

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10 Ia

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wherein, n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the same meaning as defined in claim 1.

5. A process for preparing the compound of formula (Ib) which comprises the steps of:

reacting 3-amino-4-methoxy benzoic acid (compound II) and an alcohol to obtain compound (III);

adding p-toluenesulfonic acid, benzene and 4-nitrobezonitrile thereto, refluxing the mixture at 80 to 200 °C, adding NaOCl thereto at room temperature and purifying by silica gel column chromatography to obtain compound (XI);

dissolving the compound (XI) thus obtained in an organic solvent, adding an aqueous alkali solution thereto, refluxing the mixture and purifying by silica gel column chromatography to obtain compound (XII);

dissolving the compound (XII) thus obtained in an alcohol, adding Pd/C thereto and refluxing the mixture to obtain compound (XIII);

dissolving the compound (XIII) thus obtained in an organic solvent, adding a base, 2-chloroethylmorphine and potassium iodide thereto and stirring the mixture at room temperature to obtain compound (XIV);

dissolving the compound (XIV) obtained thus in an organic solvent, adding an alkali hydrate, stirring the mixture at room temperature to obtain compound (XV);

dissolving the compound (XV) thus obtained in an organic solvent, adding 4,5-dichloro-1-(3-aminoprophyl)imidazole and a coupling agent, stirring the mixture at room temperature and purifying by silica gel column chromatography to obtain compound (XVI); and

dissolving the compound (XVI) thus obtained in MC, adding a Lewis acid thereto, stirring the mixture, concentrating the resulting solution under a reduced pressure and purifying by silica gel column chromatography to obtain compound (Ib):

XIII

wherein, n,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  have the same meaning as defined in claim 1.

6. A pharmaceutical composition for inhibiting GSK-3β comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.



## INTERNATIONAL SEARCH REPORT

International application No. PCT/KR2004/000097

A. CLA	SSIFICATION OF SUBJECT MATTER						
!	7 C07D 235/18						
According to International Patent Classification (IPC) or to both national classification and IPC  B. FIELDS SEARCHED							
Minimum documentation searched (classification system followed by classification symbols)							
IPC7 C07D	235/18	by classification symbols)					
Documentatio	on searched other than minimum documentation to the	e extent that such documents are included in the	fields searched				
Korean pate	ents and applications for inventions since 1975		Taras sometica				
Electronic dat	n base consulted during the intertnational search (nat	ne of data base and, where practicable, search ter	rms used)				
CA-onine, r	NCBI pubmed	. , =					
C. DOCUM	MENTS CONSIDERED TO BE RELEVANT						
Category*	Citation of document, with indication, where a	ppropriate, of the relevant passages	Relevant to claim No.				
Α	WO 95/07263 A (Schering Aktiengesellschaft) M	Iarch 16. 1995	1-3, 4-5, 6				
	see entire document		, , , , , ,				
A	US 5,821,258 A (Mitsui Chemicals Inc.) Oct. 13.	1998	1-3, 4-5, 6				
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A	US 6,310,082 A1 (Newcastle University Ventures see entire document	s Limited) Oct. 30. 2001	1-3, 4-5, 6				
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A	WO 2002/102978 A2 (Genentech Inc) Dec. 27, 2002 see entire document						
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	documents are listed in the continuation of Box C.	See patent family annex.					
Special cate  An document d	egories of cited documents: efining the general state of the art which is not considered	"T" later document published after the internation	al filing date or priority				
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filing date	ication or patent but published on or after the international	"X" document of particular relevance; the claimed	invention cannot be				
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means	document published prior to the international filing date but loss.						
than the prio	ority date claimed	"&" document member of the same patent family					
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